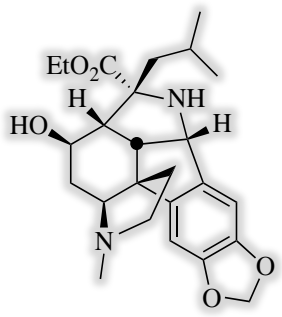
A Biomimetic Total Synthesis of the Alkaloid Gracilamine



A thesis submitted for the degree of

Doctor of Philosophy

by

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December, 2017

Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by the author during the period 2012-2016 and has not been presented for examination for any other degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.

December, 2017 ----------

Yuqian(Nadia) Gao

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Many thanks to all of you for sharing this special journey with me.

Publication and Presentations

The following publications and presentations emerged from the research work undertaken during the course of the author's PhD studies.

Publications

N. (Y). Gao, M. G. Banwell and A. C. Willis. - *Biomimetic Total Synthesis of the Pentacyclic Amaryllidaceae Alkaloid Derivative Gracilamine. Org. Lett.* **2017**, *19,* 162-165.

X. Ma, N. Gao, M. G. Banwell, P. D. Carr and A. C. Willis. - *A Total Synthesis of (±)-3-O-Demethylmacronine through Rearrangement of a Precursor Embodying the Haemanthidine Alkaloid Framework. J. Org. Chem.* **2017**, *82*, 4336-4341.

Oral Presentation

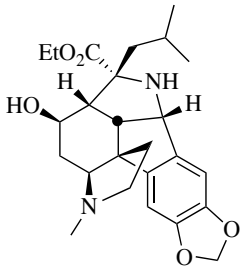
N. (Y). Gao and M. G. Banwell. - *Intramolecular Alder-ene Based Approaches to Perhydroindole-containing Alkaloids*, RACI 2014 National Congress, Adelaide, Australia, 7-12th December, 2014.

Poster Presentation

N. (Y). Gao, M. G. Banwell and A. C. Willis. - *A Biomimetic Total Synthesis of the Pentacyclic* Amaryllidaceae *Alkaloid Derivative Gracilamine*. 2016 RACI One Day Organic Symposium, Sydney, Australia, 30th November, 2016.

Abstract

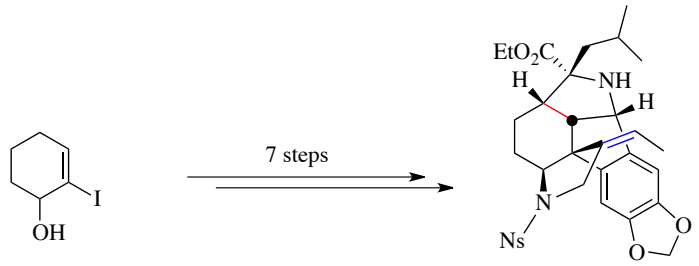
In 2005 Ünver and Kaya reported that ethanolic extraction of the dried and powdered total plant material derived from *Galanthus gracilis*, a Turkish member of the *Amaryllidaceae* family, lead to the isolation of gracilamine and to which the unprecedented structure **1.1** was assigned on the basis of extensive NMR spectroscopic and mass spectrometric analyses. This compound represents the first example of a pentacyclic dinitrogenous alkaloid isolated from the *Amaryllidaceae* family. It embodies five rings and seven stereocentres. The ethyl ester moiety associated with compound **1.1** is almost certainly an artifact of the isolation process, the naturally occurring alkaloid presumably being either another ester or the corresponding free acid. This rather complex structure together with the author's previous [BSc(Hons.)] studies made its total synthesis a topic of considerable interest.



1.1

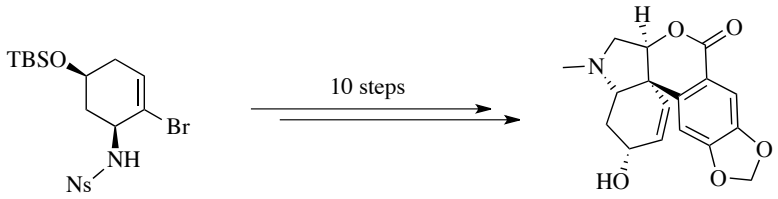
Chapter One provides a brief introduction to the isolation, structural elucidation, proposed biogenesis, and previous total syntheses of gracilamine. It also details earlier relevant work carried out by the author.

Chapter Two details a model study involving a Pd-catalysed intramolecular Alder-ene (IMAE) reaction that delivers a substrate used for testing the crucial intramolecular [3+2]cycloaddition process. By such means the basic framework, **2.24**, of gracilamine was established.



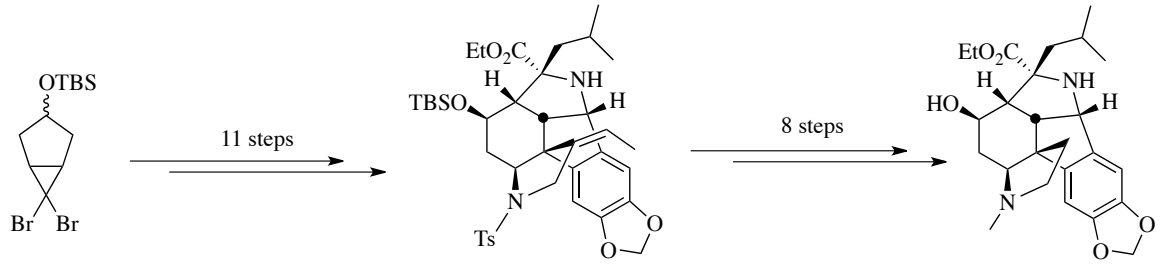
2.17 **2.24**

Chapter Three outlines the difficulties encountered in efforts to extend the above-mentioned model studies in establishing a total synthesis of gracilamine. Despite this, one of these "difficulties" could be parlayed in the establishment of a ten-step total synthesis of the racemic modification of the alkaloid (±)-3-*O*-demethylmacronine (**1.68**).



3.3 **1.68**

Chapter Four details the completion of a total synthesis of gracilamine. The final route proceeded in just eleven steps and so representing the shortest route to the title alkaloid reported thus far in this active area of research.



3.2 **4.3** **(±)-1.1**

Chapter Five presents the experimental procedures and data underpinning all of the work and conclusions detailed in Chapters Two, Three and Four.

Abbreviation

Ac	acetyl
AIBN	2,2'-azobis(*iso*-butyronitrile)
Aq	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
Boc	*t*-butoxycarbonyl
br	broad
ca.	*circa* (around)
cat.	catalytic
Cbz	carboxybenzyl
d	doublet
DCE	1,2-dichloroethane
DCM	dichloromethane
DIBAl-H	di-*iso*-butylaluminium hydride
DIPEA	di-*iso*-propylethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
dppf	1,1'-bis(diphenylphosphino)ferrocene
DMSO	dimethyl sulfoxide
EI	electron impact (mass spectrometry)
ESI	electrospray ionisation (mass spectrometry)
Et	ethyl
et al.	*et alia* (and others)
Et2O	diethyl ether
EtOAc	ethyl acetate
eV	electron volts
g	gram(s)
gem	geminal
h	hour(s)

HCl	hydrochloric acid
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
hv	light
Hz	Hertz
i.e.	*id est* (that is)
IR	infra-red
J	coupling constant (Hz)
lit.	literature value
m	multiplet
M	molar
Me	methyl
MeOH	methanol
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
m/z	mass-to-charge ratio
nm	nanometre(s)
NMR	nuclear magnetic resonance
Ns	*o*-nitrobenzenesulfonyl
NsCl	*o*-nitrobenzenesulfonyl chloride
org	organic
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PG	(unspecified) protecting group
p	*para*
Ph	phenyl

ppm	parts per million
PTSA	*p*-toluenesulfonic acid
q	quartet
quant.	quantitative
ref.	reference
R	unspecified alkyl group
R_f	thin layer chromatography retardation factor
rt	room temperature (22 °C)
s	singlet
t	triplet
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMS	trimethylsilyl
Troc	2,2,2-trichloroethyl carbonate
Ts	*p*-toluenesulfonyl
TsCl	*p*-toluenesulfonyl chloride
UV	ultra violet (spectroscopy)
v/v	unit volume per unit volume (ratio)
δ	chemical shift (parts per million)
°C	degrees Celsius
µg	microgram(s)
µL	microlitre(s)

Table of Contents

1. Chapter One: Introduction

1.1 The Pentacyclic Dinitrogenous Alkaloid Gracilamine

1.1.1 Isolation and Proposed Biogenesis of Gracilamine

In 2005 Ünver and Kaya[1] reported isolating the alkaloid gracilamine (**1.1**) from the plant *galanthus gracilis*. The compound was obtained as a colourless, amorphous solid and its structure defined as shown in **Figure 1.1**. As such this compound represents the first example of a pentacyclic dinitrogenous alkaloid isolated from the *Amaryllidaceae* family. During the course of the extraction and isolation of gracilamine (**1.1**), 5.25 kg of dried and powered total plant material was extracted using 100 L of ethanol for 40 h at room temperature. As such, the ethyl ester moiety associated with compound **1.1** is almost certainly an artifact of the isolation process, the natural occurring alkaloid presumably being either another ester or the corresponding free acid. The structure of compound **1.1** was initially investigated using ^{1}H NMR spectroscopy. Two singlets appearing at δ 6.86 ppm and 6.68 ppm in the derived spectrum are attributed to the 1,4-related aromatic protons while the two mutually coupled doublets (J = 1.1 Hz) at δ 5.95 ppm and 5.93 ppm are attributed to the geminally related and diastereotopic protons of the methylenedioxy unit. These signals helped to establish the substitution pattern of the aromatic ring. The resonances in the aliphatic region indicated the presence of six methane protons, five methylene units and four methyl groups with the lowest field of this last group of resonances suggesting the presence of a *N*-methyl residue. In the ^{13}C NMR spectrum one of the most prominent signals was a carbonyl carbon resonance appearing at δ 175.8 ppm. This, when considered alongside the appearance of a strong carbonyl stretching band at 1715 cm^{-1} in the IR spectrum, suggested the presence of an ester group. After detailed analysis involving ESI-MS, CI-MS, IR, UV and 2D NMR spectrometric and spectroscopic studies, structure **1.1** was proposed for gracilamine although the stereochemistry of the 2°-hydroxyl group remain undefined at that point. In 2012, Ma and co-workers[2] reported the first total synthesis of (±)-gracilamine and so establishing the illustrated β-configuration of

this group.

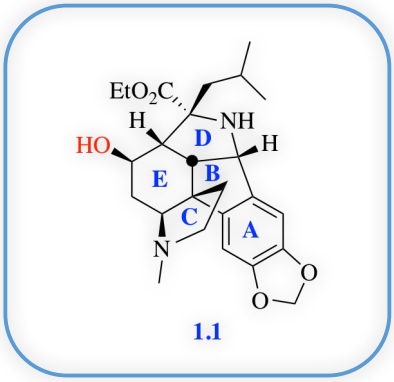


Figure 1.1: The Flowers of the Plant* Galanthus gracilis *and the Structure of the Derived Alkaloid Gracilamine (1.1).

A part of the process of elucidating the structure of gracilamine, Ünver and Kaya proposed the pathway shown in **Figure 1.2** for its biogenesis. This starts with the fragmentation of the tazattine **1.2** and thus forming the isomeric aldehyde **1.3** that itself engages in a Schiff base condensation reaction with the amino acid lysine **1.4** to give imine **1.5**. Re-organization of this last species would give rise to an azomethine ylide **1.6** that could then engage in a facially selective [3+2]cycloaddition reaction with the double bond of the pendant hexahydroindole moiety and thus forming the carboxylic acid corresponding to gracilamine (**1.1**). The validity of the latter elements of this proposal is supported by the elegant work of Ma and co-workers[2] who developed a biomimetic synthesis of this alkaloid framework. Details of this work are presented below.

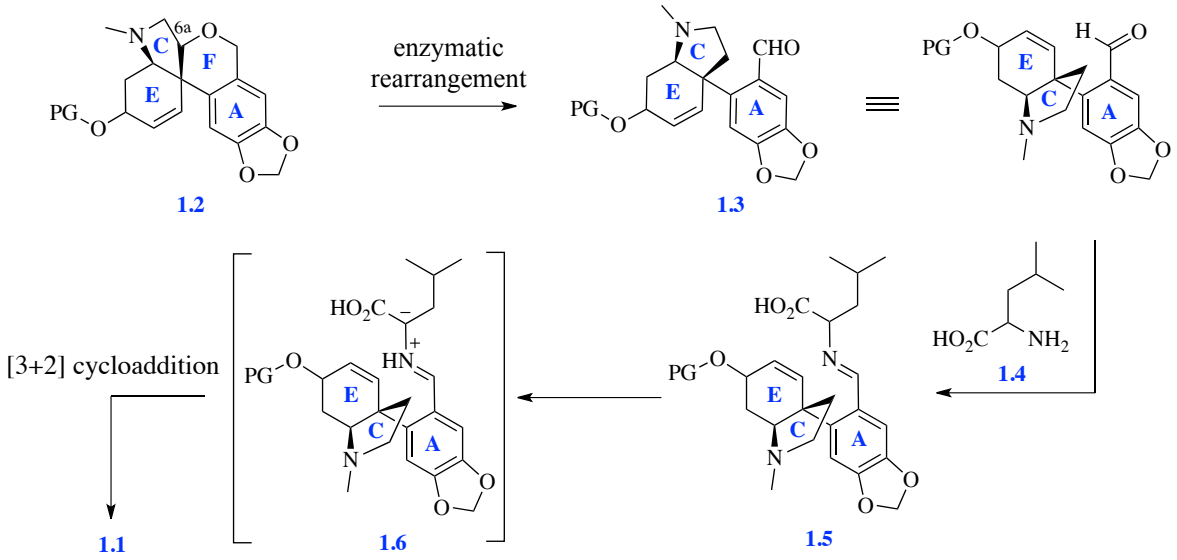


Figure 1.2: A Possible Biogenetic Pathway Leading to Gracilamine (1.1).

1.1.2. THE BIOLOGICAL PROPERTIES OF THE *AMARYLLIDACEAE* ALKALOIDS

Plants from the *Amaryllidaceae* family include *ca.* 65 genera and about 860 species. They are among the top twenty of the most widely applied families of medicinal plant.[3] A large number of pharmacologically active compounds have been derived from this family including alkaloids, phenols, lectins and peptides. To date around 500 structurally diverse alkaloids have been isolated from plants of the *Amaryllidaceae* family and many of them have shown interesting biological activities including anti-tumour, anti-viral, and anti-inflammatory properties. Others have been shown to display immunostimulatory and acetylcholinesterase inhibitory activities.[3] Such is their potency and efficacy that some of these alkaloids have been approved for clinical use (**Figure 1.3**). Perhaps most notably, galanthamine (**1.7**), a particularly well-known alkaloid of this class, has been employed in a range of countries for the treatment of Alzheimer's disease. It shows long-acting, selective, reversible and competitive acetylcholinesterase inhibitory activity that lasts even after termination of treatment.[4] Another well-known *Amaryllidaceae* alkaloid is pancratistatin

(**1.8**). This exhibits potent apoptotic activity against cancer cells without being cytotoxic to healthy ones.[5] In order to improve its aqueous solubility and transport to tumours (where it exerts anti-angiogenic effects) this has been converted into a 3,4-cyclic phosphate derivative that acts as a prodrug.[6] Lycorine (**1.9**), homelycorine (**1.10**), trisphaeridine (**1.11**) and haemanthamine (**1.12**) have each been subjected to *in vitro* evaluation of their capacities to inhibit the growth of HIV-1 within the MT4 human T cell line and thus shown to possess high anti-retroviral activities (IC_{50} = 0.4-7.3 μg mL^{-1}) as well as low therapeutic indices (TI_{50} = 1.3-1.9).[3] As the first example of pentacyclic dinitrogenous alkaloid, the biological activities of gracilamine (**1.1**) would be very interesting to determine. To date this has not been possible because of its limited availability from natural sources. As such, and given its novel structural features, gracilamine (**1.1**) represents a very interesting target for total synthesis.

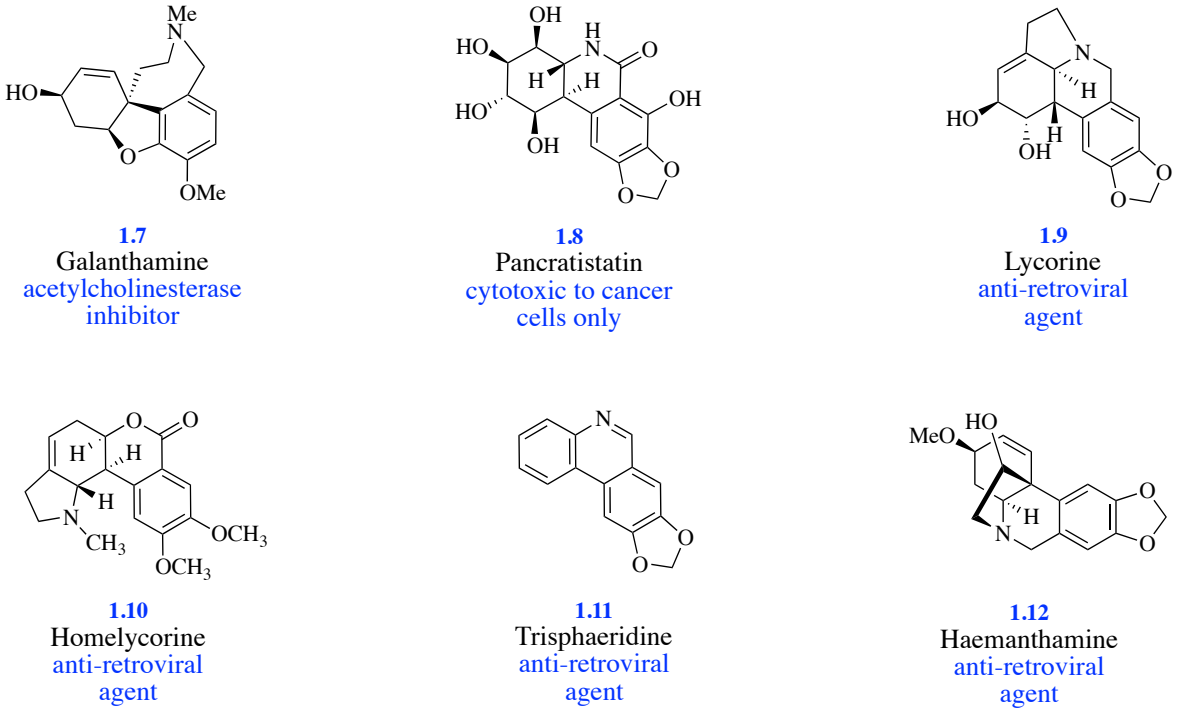
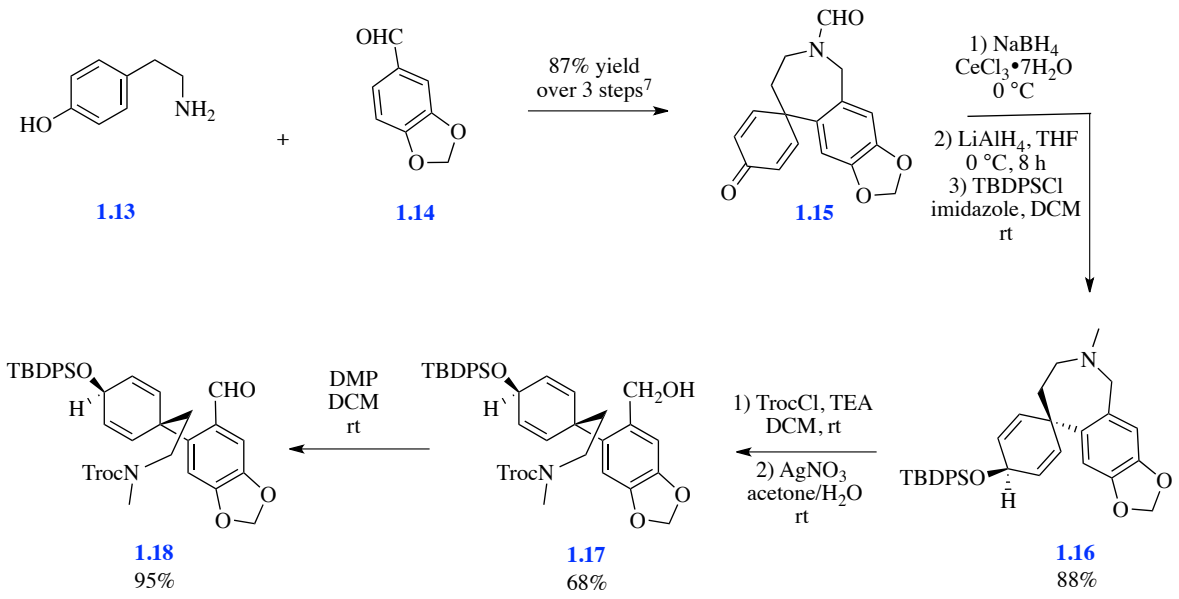


Figure 1.3: Examples of Pharmacologically Active* Amaryllidaceae *Alkaloids.

1.2 Previous Syntheses of Gracilamine

1.2.1. The First Total Synthesis of (±)-Gracilamine (2012)

In 2012 Ma and co-workers[2] reported the first total synthesis of the racemic modification of gracilamine that cleverly exploited the biogenetic proposals of Ünver and Kaya. As shown in **Scheme 1.1**, their route started with tyramine (**1.13**) and piperonal (**1.14**) and, following Node's procedure, derivative **1.15** was generated in 87% yield over 3 steps.[7] Luche-type reduction of compound **1.15** (to give the corresponding methylamine) and a further reduction with $LiAlH_4$ followed by protection of the ensuing alcohol with TBDPSCl then delivered silyl ether **1.16**. The seven-membered ring associated with compound **1.16** was cleaved with TrocCl/TEA and the resulting benzyl chloride immediately treated with $AgNO_3$ in aqueous acetone to provide the corresponding benzyl alcohol **1.17** that was obtained in 68% yield over the two steps involved. Oxidation of compound **1.17** with the Dess–Martin-periodinane then furnished aldehyde **1.18**, the key substrate required for setting up the biomimetic and intramolecular [3+2]cycloaddition reaction.



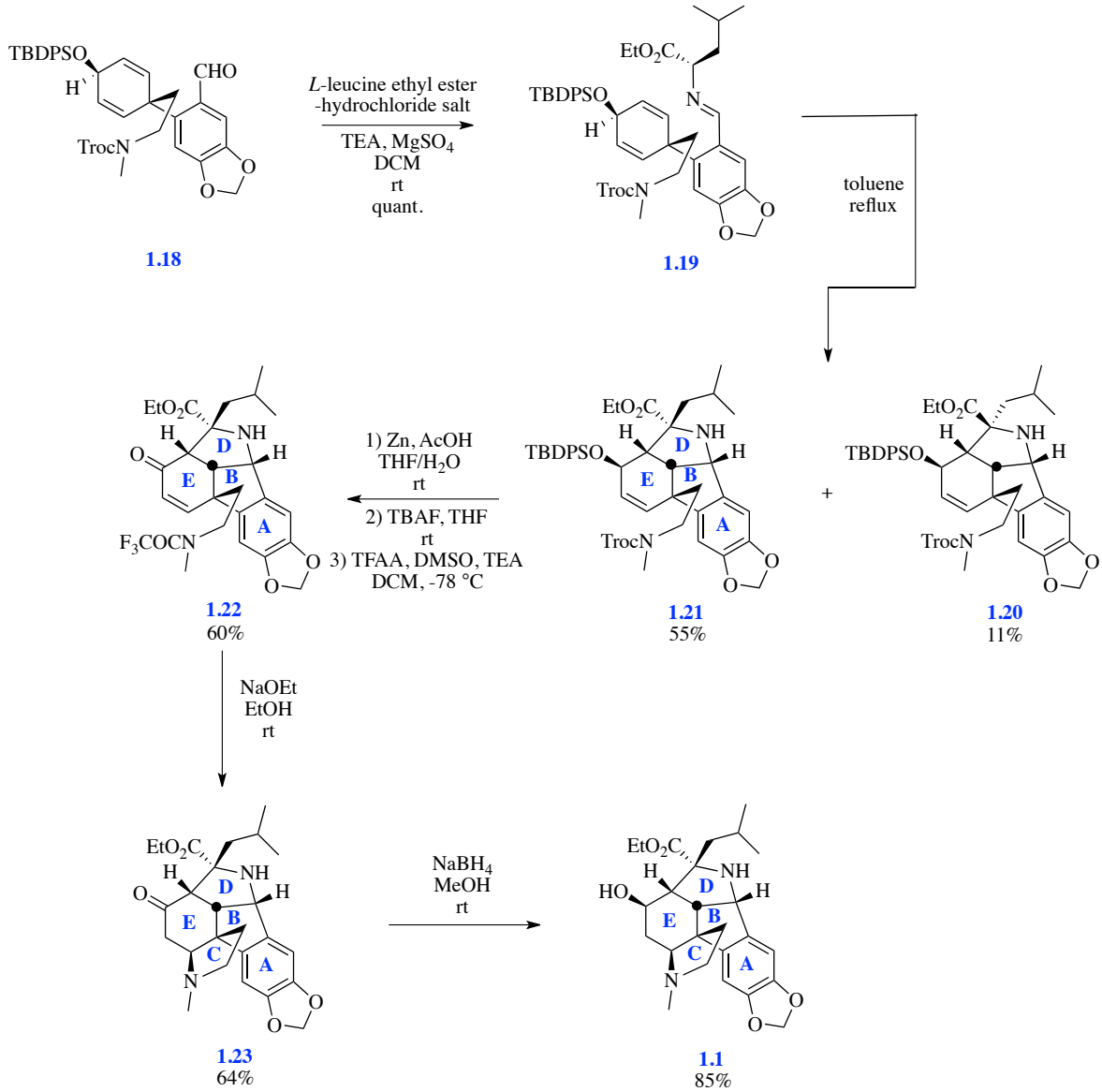
Scheme 1.1: Ma's Synthesis Part 1-

Formation of the Precursor for the Intramolecular [3+2]Cycloaddition Reaction.

In order to test the key step of Ünver and Kaya's biosynthetic hypothesis (**Scheme 1.2**), condensation of aldehyde **1.18** with *L*-leucine ethyl ester hydrochloride salt was carried out and so producing the imine **1.19** required for the intramolecular [3+2]cycloaddition reaction.[8] In the event, on heating compound **1.19** under reflux in toluene then adducts **1.20** and **1.21** were formed in 66% combined yield with the major one, **1.21**, shown to be that incorporating the required ABDE ring system of gracilamine. This impressive transformation has thus resulted in the assembly of two new rings and four stereocenters in a single chemical event. An intramolecular hetero-Michael addition reaction was then employed to establish the C-ring. Thus, two-fold deprotection of compound **1.21** using Zn/AcOH and TBAF afforded the corresponding amino alcohol that was subject to a Swern oxidation using $(CF_3CO)_2O$ and DMSO and so producing the enone **1.22** (60%) embodying a trifluoroacetamide unit. Cleavage of the latter moiety using NaOEt in ethanol then delivered the cyclization product **1.23** in 64% yield. Finally, stereoselective reduction of the E-ring carbonyl group served to introduce the required β-configured hydroxyl group and, thereby, (±)-gracilamine (85%). The structure of this product was confirmed by single-crystal X-ray analysis. Since all of the other spectral data obtained on this synthetically

derived material matched those reported for the "natural" product, the relative configuration of gracilamine was determined to be as shown in structure **1.1**.

Overall, Ma and co-workers achieved the first total synthesis of (±)-gracilamine (**1.1**) in 17 linear steps and 4.5% overall yield. The successful implementation of the biomimetic intramolecular [3+2]cycloaddition reaction strongly supports Ünver and Kaya's proposals concerning the biogenesis of the gracilamine framework.

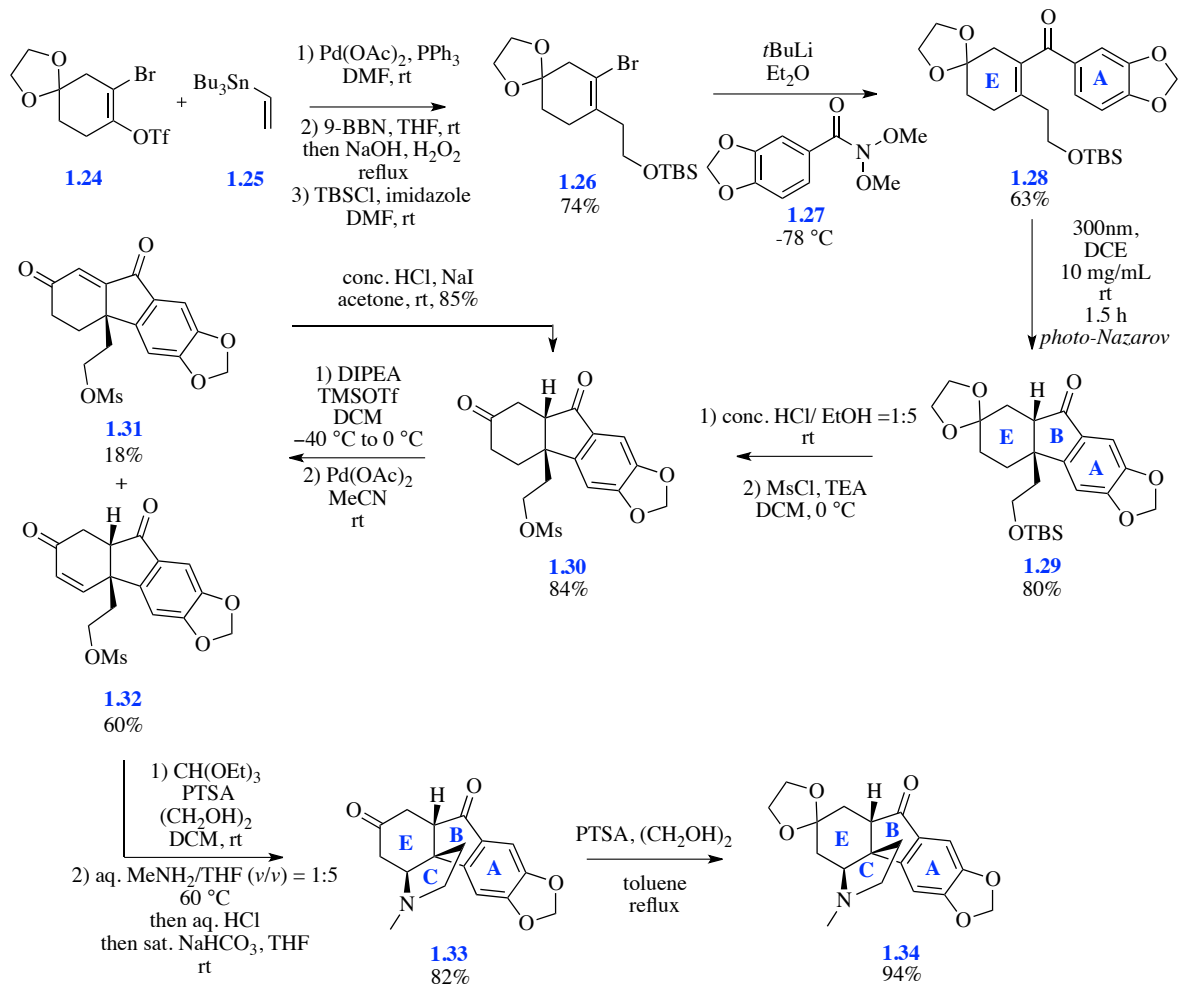


Scheme 1.2: Ma's Synthesis Part 2-Completion of Gracilamine (1.1).

1.2.2. The Second Total Synthesis of (±)-Gracilamine (2014)

In 2014 Gao and co-workers[9] detailed an AE → AEB → AEBC → AEBCD ring assembly process involving photo-Nazarov, intramolecular hetero-Michael, and intramolecular Mannich reactions as key events in their synthesis of gracilamine **1.1**.

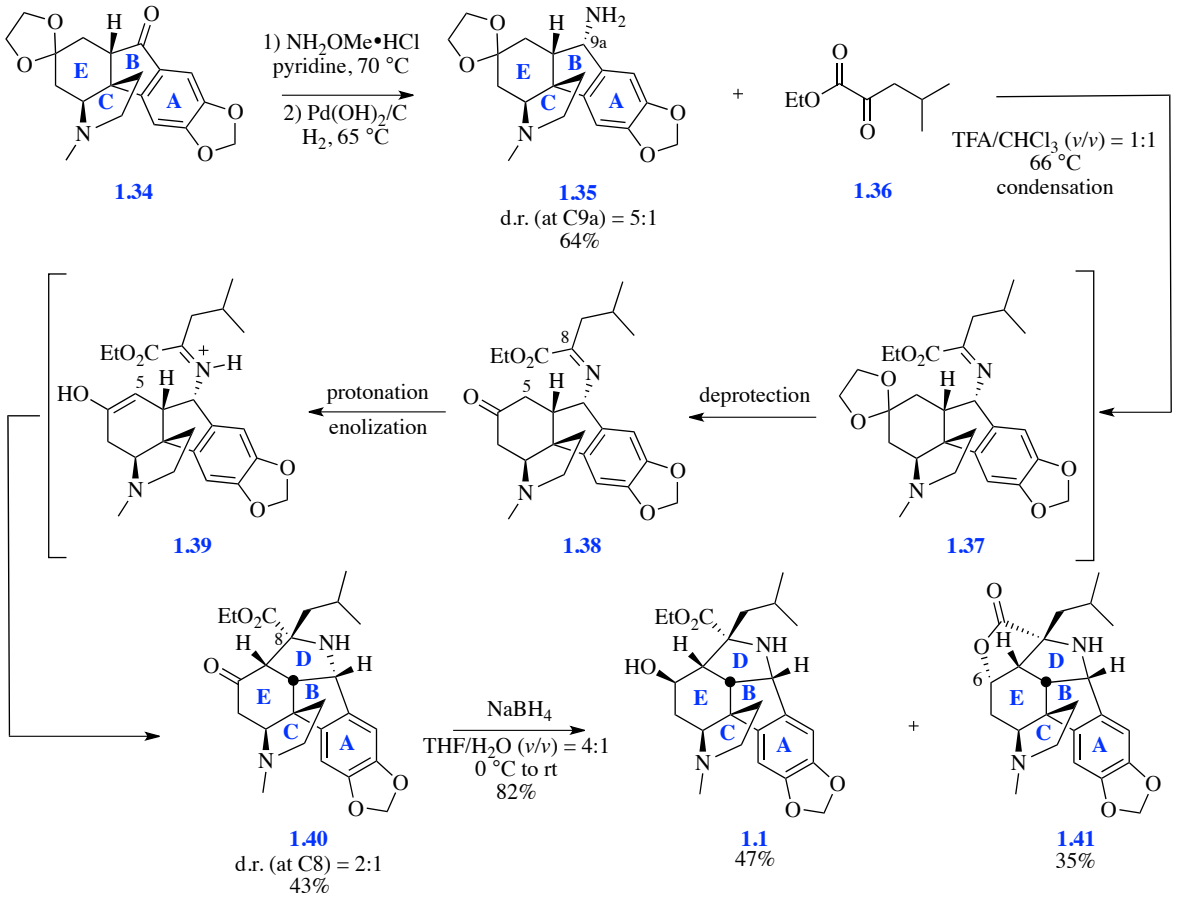
Their synthesis began with the construction of the AEBC ring skeleton (**Scheme 1.3**). The starting bromoenol triflate **1.24** was prepared using a reported three-step process[10] and Stille coupling of this with tributyl(vinyl)stannane (**1.25**) followed by a two-step reaction sequence involving hydroboration-oxidation then protection furnished compound **1.26** in 74% yield. Treatment of this last compound with *t*-BuLi followed by reaction of the lithio-species so formed with the Weinreb amide **1.27** generated the enone **1.28** (63%), the substrate for the key Nazarov reaction. In the fully optimized photo-Nazarov process,[11] a solution of compound **1.28** in dichloroethane (DCE) was irradiated with 300 nm wavelength light for 1.5 hours at room temperature to generate compound **1.29** (80%) containing the B-ring of gracilamine. In order to construct the D ring, compound **1.29** was converted into congener **1.30** (84%) via a deprotection and mesylation sequence. By applying the Saegusa-Ito oxidation condition[12] to this last compound a chromatographically separable mixture of enones **1.31** and **1.32** was obtained in 78% combined yield. The unwanted regioisomer **1.31** could be easily converted into "starting material" **1.30** in 85% yield by treatment with NaI and conc. HCl. After protection, amination, and 1,4-addition of compound **1.32**, ring C was successfully installed and thereby producing compound **1.33** in 82% overall yield. Selective protection of the E-ring carbonyl group of compound **1.33** then gave compound **1.34** in 94% yield.



Scheme 1.3: Gao's Synthesis Part 1- Assembling the ABCE Rings of Gracilamine (1.1).

Gao's assembly of the D ring associated the gracilamine skeleton is shown in **Scheme 1.4** and started with the condensation of ketone **1.34** with *O*-methylhydroxylamine to give the corresponding *O*-methyl oxime that was itself hydrogenated to give amine **1.35** (d.r. = 5:1 at C9a). In order to apply the final key step, a solution of compounds **1.35** and **1.36** in TFA/$CHCl_3$ (1:1, *v/v*) was heated to 66 °C and so affording the cyclized product **1.40** directly and as a mixture of two diastereoisomers (d.r. = 2:1 at C8). The D ring was finally generated through bond formation between C5 and C8 and so generating a quaternary carbon at the latter centre. This involved condensation of compounds **1.35** and **1.36** (to produce imine **1.37**), acetal group removal (to obtain ketone **1.38**), acid-promoted iminium

cation formation (to produce **1.39**) and, finally, an intramolecular Mannich annulation reaction that completed formation of the D ring. Reduction of the carbonyl group within cycloadduct **1.40** using sodium borohydride in tetrahydrofuran/water afforded a chromatographically separable mixture of the racemic modification of gracilamine **1.1** (47%) and the lactone **1.41** (35%), the latter presumably arising through cyclisation of the α-epimer at C6. The structures of both products were confirmed by single-crystal X-ray analyses while the spectral data derived from the former product matched those reported by Ma and co-workers.[2]



Scheme 1.4: Completion of the Synthesis of (±)-Gracilamine (1.1) by Gao and Co-workers.

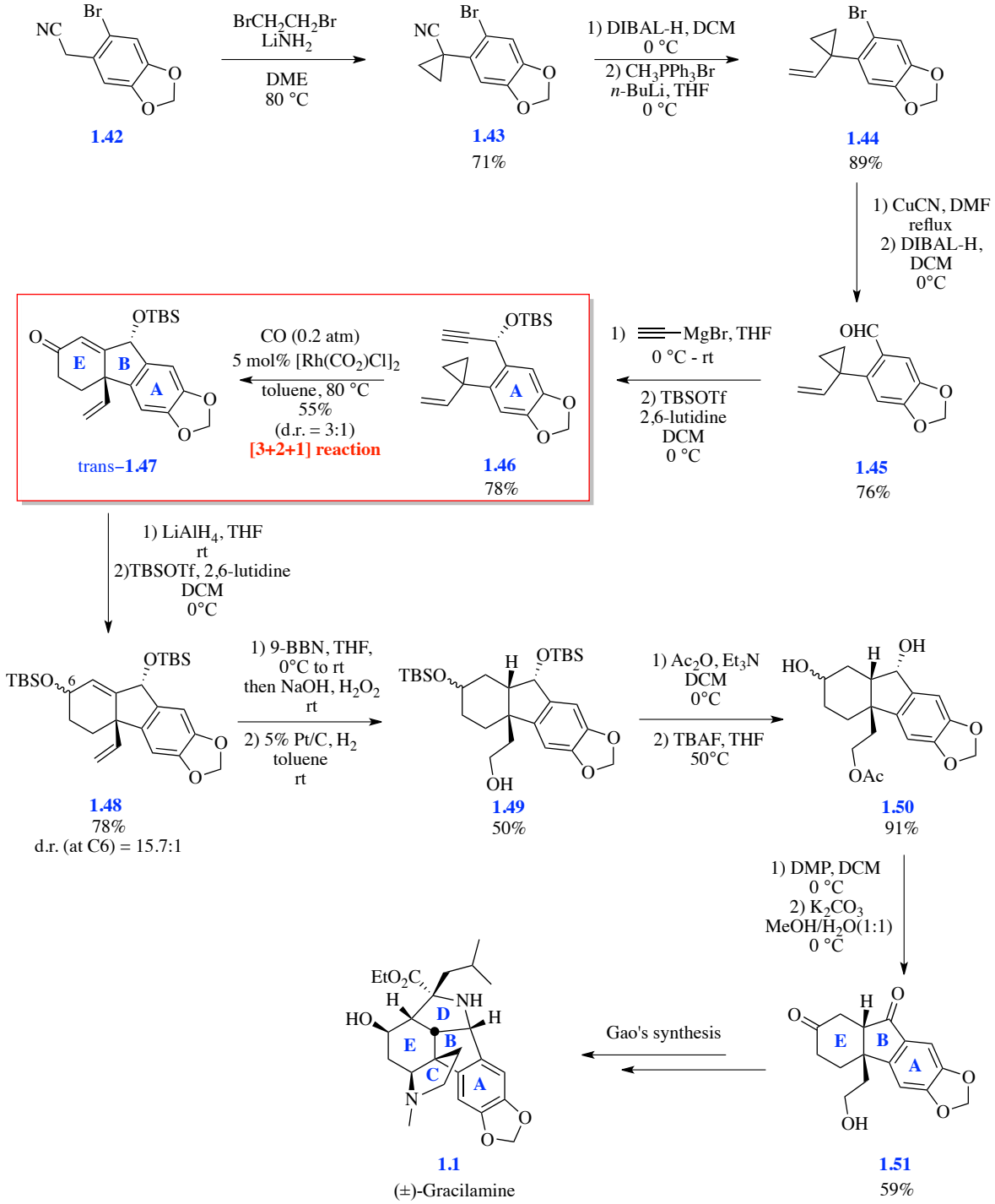
1.2.3 Yu's Formal Synthesis of (±)-Gracilamine (2016)

In 2016 Yu and co-workers reported a formal total synthesis of the title compound.[13] They assembled the target in an enantioselective fashion using a Rh(I)-catalyzed [3+2+1]cycloaddition reaction[14] to obtain an AEB-containing system associated with Gao's synthesis. So, starting with the known bromide **1.42**[15] this was treated with ethylene dibromide and lithium amide in dichloroethane[16] and the cyclopropane **1.43** was thereby formed in 71% yield (**Scheme 1.5**). Reduction of the associated nitrile group using DIBAl-H followed by aqueous work-up then provided the corresponding aldehyde that was converted into vinyl cyclopropane **1.44** (89%) under standard Wittig conditions. In order to introduce the propargyl moiety required for a Rh(I)-catalyzed [3+2+1]cycloaddition reaction, the bromo moiety was firstly subject to a cyanation reaction and the product nitrile reduced to the corresponding aldehyde **1.45** (76%). This last compound was engaged in a Grignard addition with ethynylmagnesium bromide and the hydroxyl group associated with the resulting propargylic alcohol then protected as a TBS-ether to give the target substrate **1.46** in 78% yield over the two steps involved.

The key [3+2+1]cycloaddition was performed in the presence of 5 mol % of rhodium catalyst under an atmosphere of CO and N_2 and so delivering the desired 5/6 ring-fused product **1.47** in 55% yield and as a 3:1 admixture with its diastereoisomer.[i] The preferential formation of compound **1.47** may result from the repulsion between the OTBS group and the vinyl moiety in the transition state leading to its isomer. The carbonyl group associated with enone **1.47** was reduced with lithium aluminum hydride and the resulting allylic alcohol treated with TBSOTf and 2,6-lutidine to provide the corresponding TBS-ether **1.48** in 78% yield and as a *ca*. 16:1 mixture of C6-epimers. The exocyclic double bond within product **1.48** was subjected to a hydroboration-oxidation reaction using 9-BBN[17] and so giving the corresponding primary alcohol. The associated endocyclic double bond was then hydrogenated using dihydrogen and Pt/C and thus affording compound **1.49** in 50% overall yield. This primary alcohol was then protected as the corresponding acetate and the two associated TBS ethers were cleaved with TBAF to afford diol **1.50** in 91% yield (over two

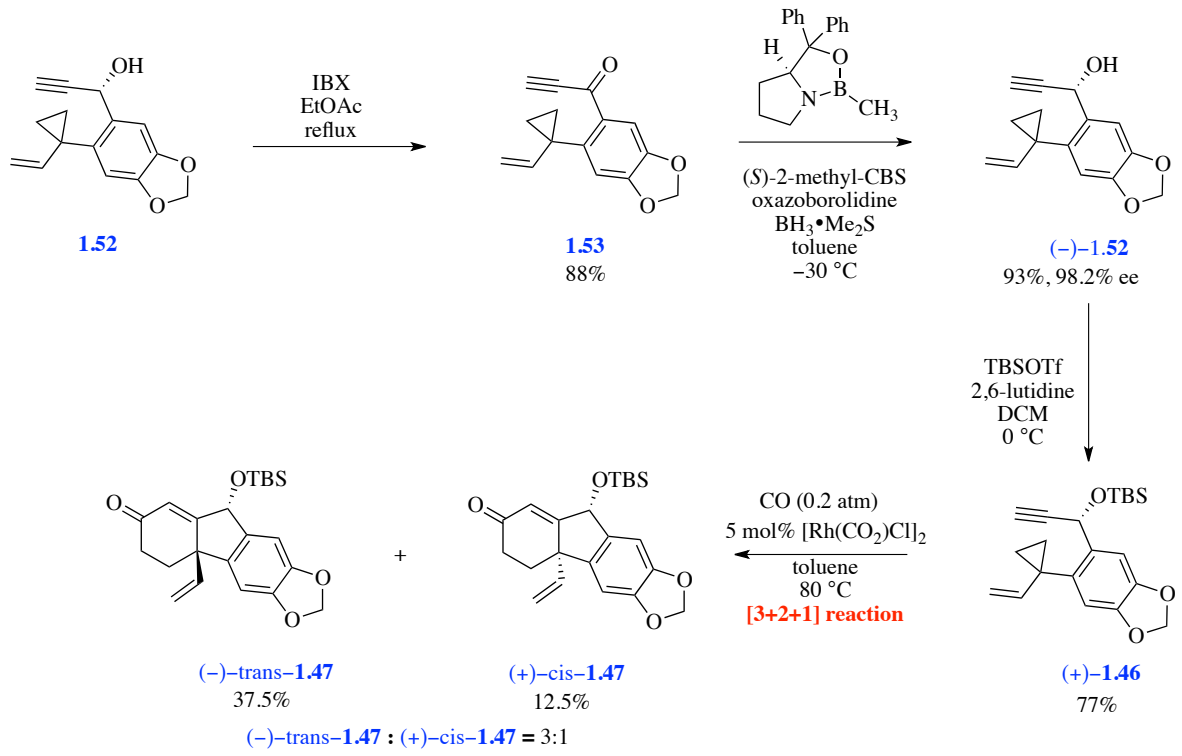
[i] See the red highlight frame in **Scheme 1.5**.

steps). Diol **1.50** was oxidized with the Dess-Martin periodinane to form the corresponding diketone that was treated with potassium carbonate so as to generate compound **1.51** in 59% yield (over 2 steps). The NMR spectral data acquired on this last compound matched those report for the same intermediate associated with Gao's synthesis.[9] As such a formal total synthesis of (±)-gracilamine (**1.1**) had been achieved.



Scheme 1.5: Yu's Formal Synthesis of (±)-Gracilamine (1.1) Through the Acquisition of a Key Intermediate, 1.51, Associated with Gao's Work.

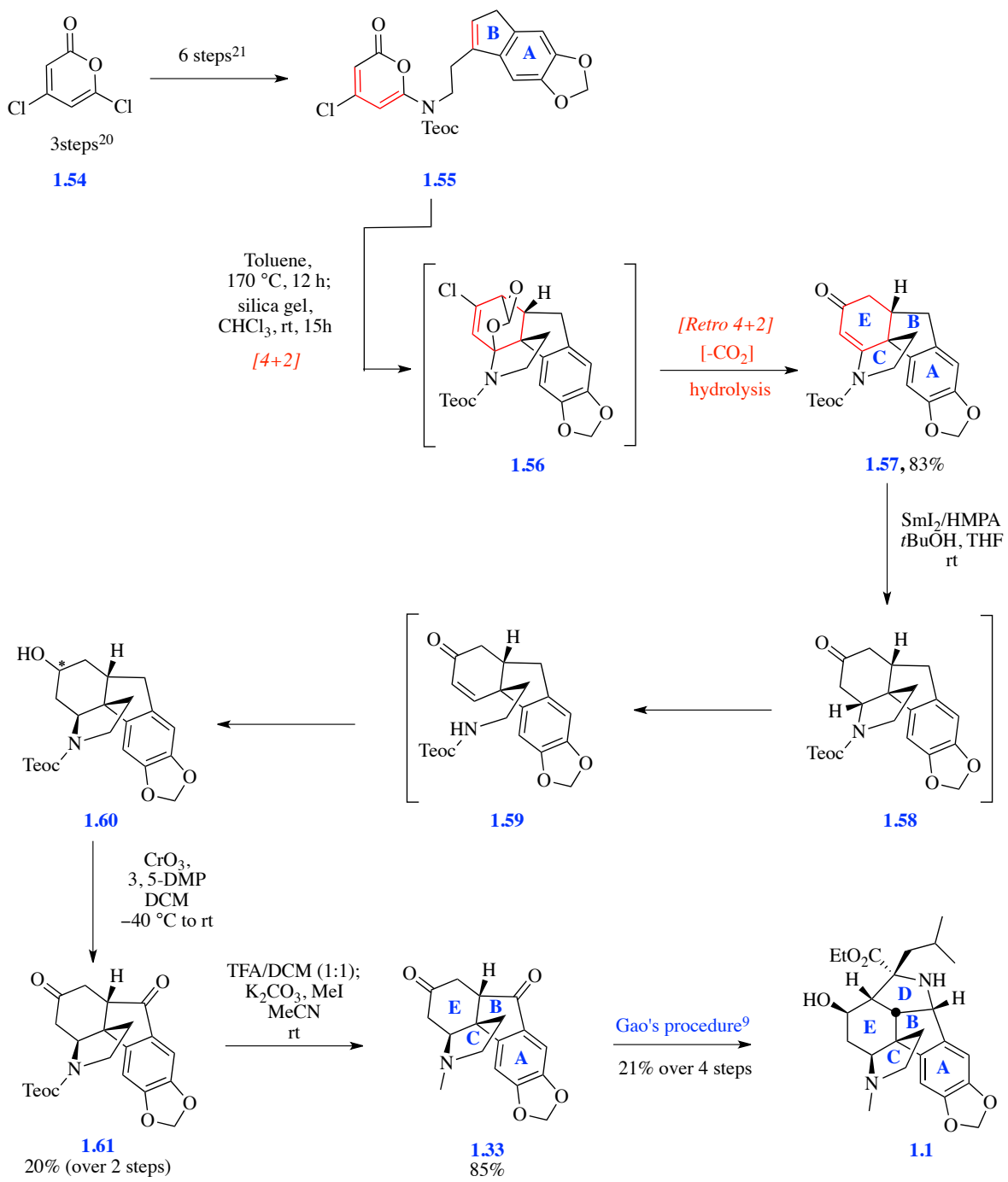
Yu and co-workers[13] were able to modify their route so as to make the same key intermediate in an enantioselective manner (**Scheme 1.6**). Thus, the previously synthesized and racemic propargyl alcohol **1.52** was oxidized to ketone **1.53** that then was reduced using the (*S*)-form of the CBS (Corey-Bakshi-Shibata) reagent[18] in conjunction with BH_3•Me_2S and so producing the alcohol (−)-**1.52** in 98% *ee*. TBS-protection of this alcohol and engagement of the product ether (+)-**1.46** in the previously performed [3+2+1]cycloaddition reaction gave a mixture of the (−)-*trans*-**1.47** and (+)-*cis*-**1.47** forms of the product 2-cyclohexen-1-one in a combined yield of 50%. Both of these could be carried forward in the production of the chiral non-racemic diketone **1.51**. However, this second facet of the Yu group's work is of only limited utility because it wasn't carried forward to the relevant form of gracilamine and so the absolute configuration of the alkaloid remained undefined at this stage.



Scheme 1.6: Yu's Formal Synthesis Towards Enantiomer Pure Gracilamine (1.1).

1.2.4 Snyder's Formal Synthesis of (±)-Gracilamine (2016)

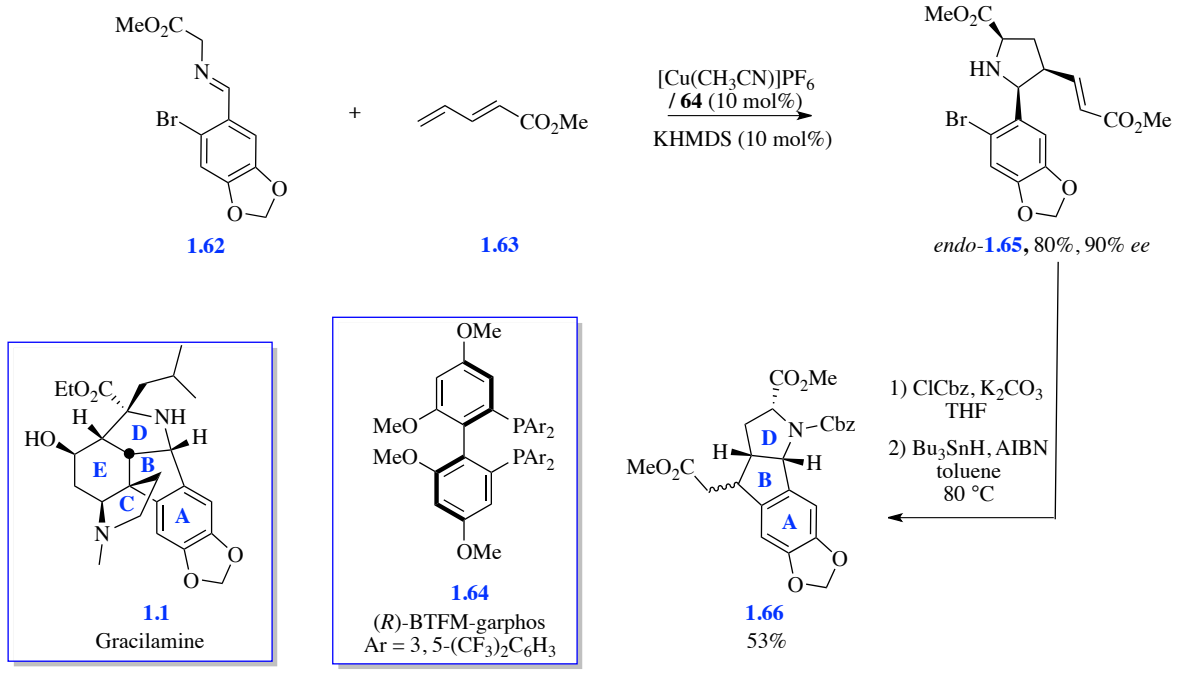
In 2016, Snyder and co-workers[19] reported an elegant route to a methylene-bridged C3a-arylated hexahydroindole embodying the AEBC-framework of (±)-gracilamine and which could be elaborated to an advanced intermediate associated with Gao's total synthesis. The key step in this synthesis was an intramolecular Diels-Alder reaction involving a pyrone as the diene moiety. Thus, as shown in **Scheme 1.7**, the synthesis started with 4,6-dichloropyrone (**1.54**) that could be readily prepared in three steps on a multigram scale.[20] Following a six-step[21] sequence, an amine-containing linkage between the pyrone and AB ring system of the target was installed to afford compound **1.55**. This was then heated at 170 °C in toluene under microwave irradiation for 12 hours before being treated with silica gel in chloroform at room temperature. Under such conditions, an intermolecular pyrone-based Diels-Alder reaction ensued and this was followed by a cycloreversion reaction involving the loss of CO_2 and then a hydrolysis to afford tetracycle **1.57** (83%) embodying the AEBC-ring system of target (±)-**1.1**. Reduction of compound **1.57** with SmI_2 and HMPA[22] then delivered, via intermediates **1.58** and **1.59**, alcohol **1.60** embodying the full carbocyclic framework of the target alkaloid. Salmond-type oxidation[23] of alcohol **1.60** then gave diketone **1.61** (20% overall from ketone **1.57**) and the application of a one-pot Teoc deprotection and methylation[24] reaction sequence to this last compound provided congener **1.33** (85%), an advanced intermediate associated with Gao's synthesis of gracilamine. In an overall sense, then, the authors were able to complete a total synthesis of gracilamine (**1.1**) in 14 steps from the commercially available pyrone **1.54**.



Scheme 1.7: Synder's Formal Synthesis of (±)-Gracilamine (1.1) Through the Acquisition of a Key Intermediate, 1.33, Associated with Gao's Work.

1.2.5 Adrio's Asymmetric Synthesis of the ABD-Core of (±)-Gracilamine (2015)

In 2015 by Adrio and co-workers[25] reported a rather concise synthesis of a 1,2,3,3a,4,8b-hexahydroindeno[1,2-*b*]pyrrole that embodies key elements of the ABD-ring system of (±)-gracilamine (**1.1**). The key step in their work was the 1,3-dipolar cycloaddition of an azomethine ylide to an activated olefin.[26] Thus, as shown in **Scheme 1.8**, a [3+2]cycloaddition reaction between imino-ester **1.62** and diene **1.63** using copper and ligand **1.64** as a catalyst source led to the *endo*-configured pyrrolidine **1.65** which was obtained in 80% yield and 90% *ee*. Protection of the amine residue within this adduct as its Cbz derivative and engagement of this in a 5-*exo-trig* radical cyclization process using tributyltin hydride/2,2'-azobis(*iso*-butyronitrile) led to the tetracyclic derivative **1.66** in 53% overall yield and as 1:1 mixture of diastereoisomers. By such direct means a suitably functionalized form of the ABD-ring system of gracilamine was assembled.



Scheme 1.8: Adrio's Enantioselective Preparation of the ABD-Core of the Alkaloid (±)-Gracilamine (1.1).

1.2.6 Summary of Previous Total Syntheses/Formal Total Syntheses of Garcilamine

A summary of all the above-mentioned approaches to gracilamine (**1.1**) is presented in **Figure 1.4**. Thus, as noted earlier, in 2012 Ma and co-workers[2] reported that a spiro-ring fused cyclohexa-1,4-diene containing a tethered Schiff-base engaged in a thermally-induced and stereoselective intramolecular [3+2]cycloaddition reaction and so giving compound **1.19** that incorporates the ABDE-ring system of gracilamine (**1.1**). An intramolecular hetero-Michael addition reaction was then employed to establish the final C-ring. In 2014 Gao and co-workers[9] detailed an AE → AEB → AEBC → AEBCD ring-assembly process involving photo-Nazarov, intramolecular hetero-Michael, and intramolecular Mannich reactions as key events in their synthesis of the target natural product. One year later, Adrio and co-workers[25] reported a three-step and asymmetric synthesis of a 1,2,3,3a,4,8b-hexahydroindeno[1,2-b]pyrrole (**1.66**) that embodies key elements of the ABD-core of gracilamine but have not reported, at least to date, taking this work any further. A formal total synthesis of gracilamine was realized by Yu and co-workers[14] who assembled, in an enantioselective fashion using a Rh(I)-catalyzed [3+2+1]cycloaddition reaction, an AEB-containing system (compound **1.51**) associated with Gao's synthesis. Finally, and very recently, Snyder and co workers[19] described a pyrone-based intramolecular Diels−Alder route to a methylene-bridged C3a-arylated hexahydroindole containing the AEBC-framework of (±)-gracilamine (compound **1.33**) and that could be elaborated to an advanced intermediate associated with Gao's total synthesis.

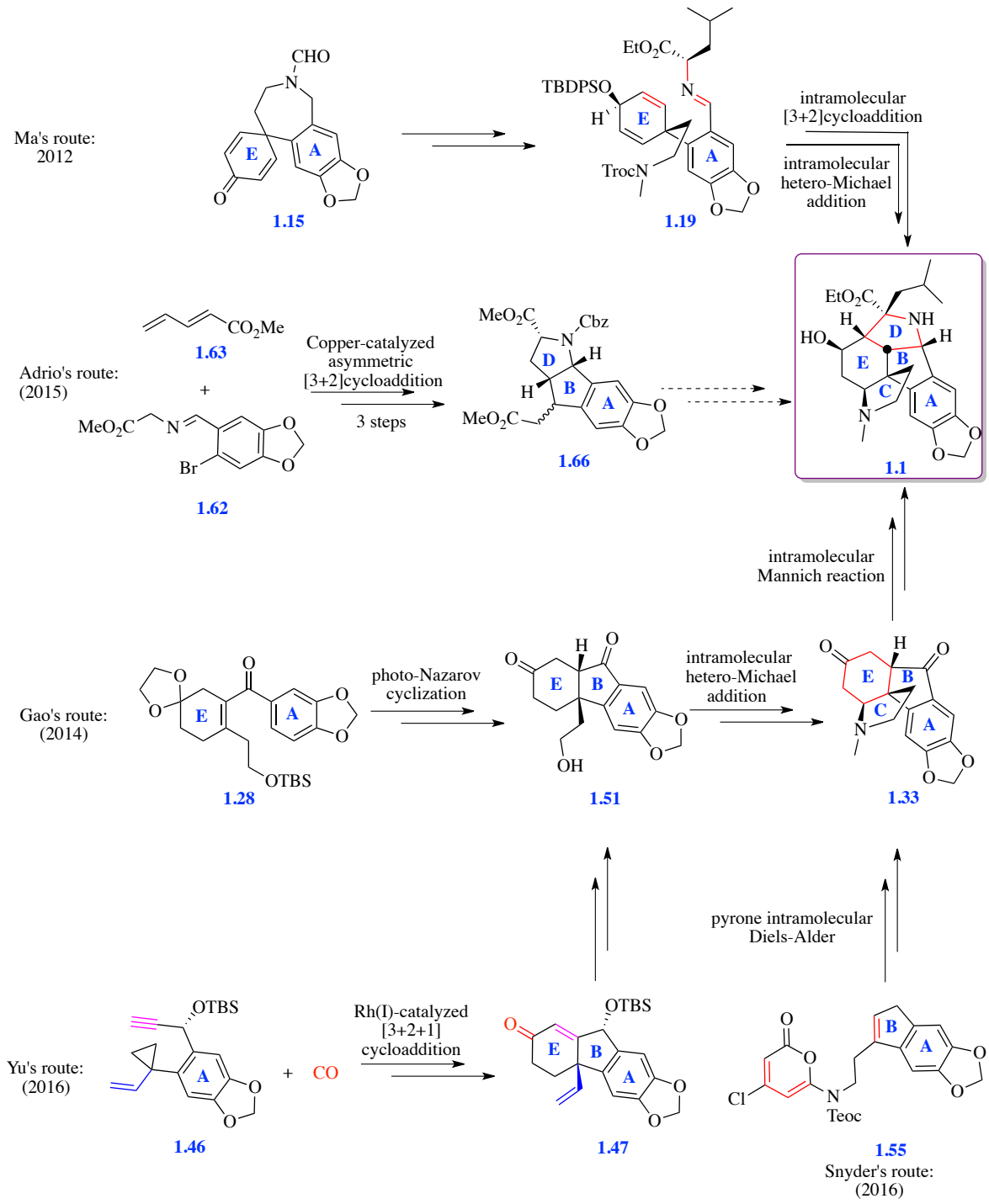
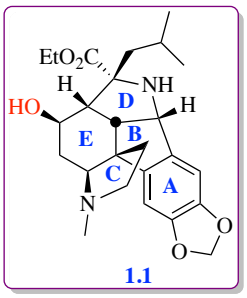


Figure 1.4: Outline of Approaches to the Synthesis of Gracilamine (1.1) Carried Out by the Groups of Ma, Gao, Adrio, Yu, and Synder.

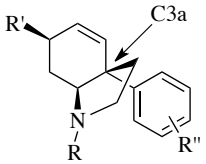
1.2 Overview of the Contents of the Remaining Parts of this Thesis

The work that is described in the body of this thesis was directed towards establishing a total synthesis of gracilamine using the methodology that has been developed within the Banwell Group and involving a Pd(II)-catalysed IMAE reaction as the key step to prepare the C3a-arylhexahydroindole unit **1.67**. Compound **1.67** was then to be employed as the substrate in a process mimicking the proposed biosynthetic pathway described above {and involving an intramolecular [3+2]cycloaddition reaction} so as to assemble the remaining parts of the molecular framework associated with gracilamine (**1.1**).

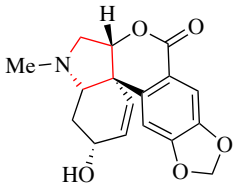
Accordingly, the first part of the work reported in the remaining chapters was directed towards constructing, using model systems, the ABCDE ring system of gracilamine by using the [3+2]cycloaddition process and the second was to be focused on constructing the fully functionalized framework of gracilamine if the initial (model) studies were successful. Accordingly, Chapter Two details the author's work involved in conducting a relevant "model study" while the extension of these to (±)-gracilamine (**1.1**) is presented in Chapters Three and Four. Also detailed in Chapter Three is the exploitation of some unexpected cyclisation reactions encountered during these studies in the synthesis of the racemic modification of the natural product 3-*O*-demethyl-macronine (**1.68**). The remaining parts of this Chapter (One) highlight the previous, relevant work undertaken by the author.



1.1



1.67

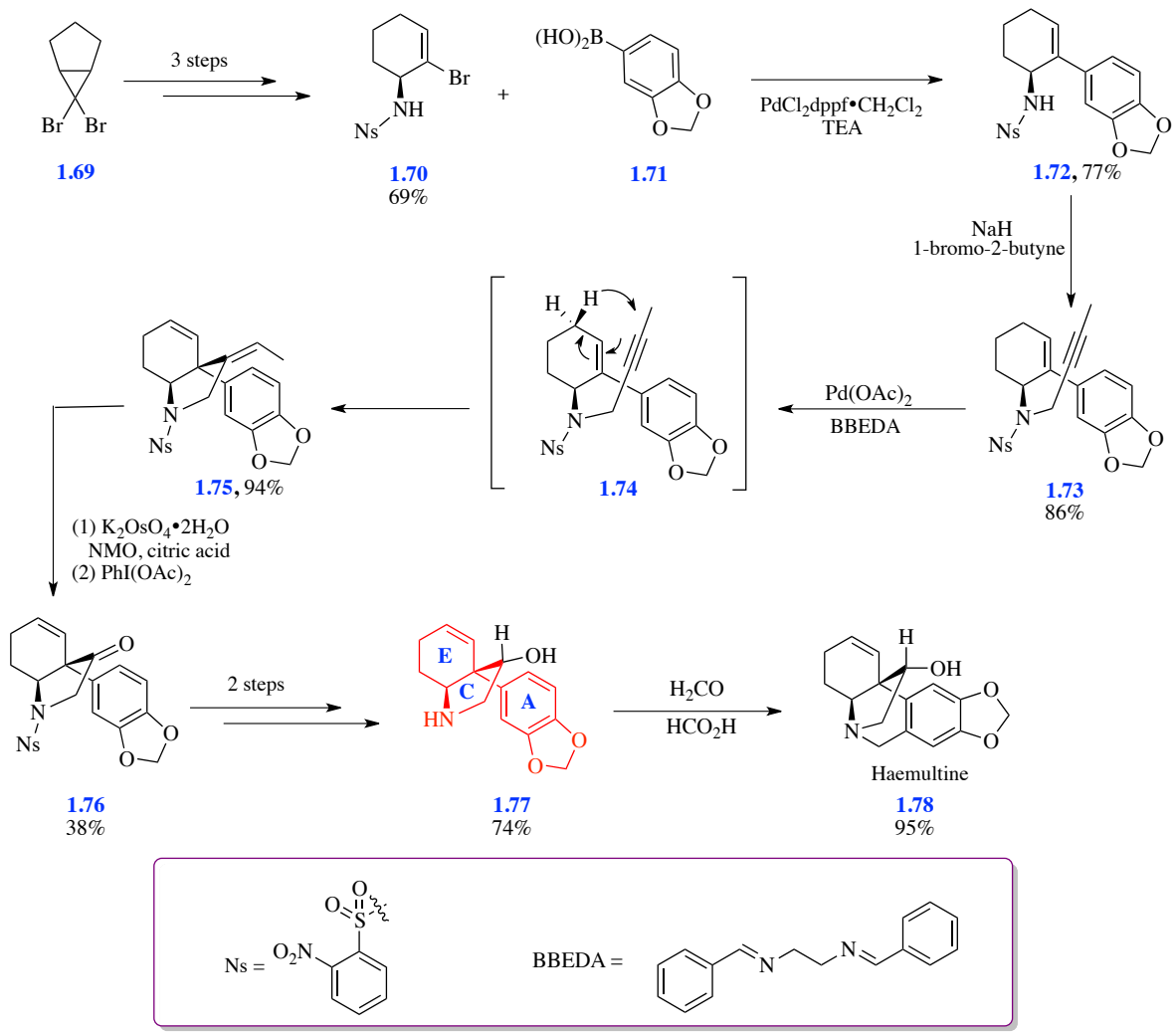


1.68

Figure 1.5: Structure of Gracilamine 1.1, 3-O-Demethylmacronine (1.68) and the C3a-Arylhexahydroindole Unit 1.67.

1.3 Earlier Relevant Work Carried out by the Author

In 2010, the author co-published[27] details of a total synthesis of haemultine that emerged from her studies for the BSc(Hons.) degree (**Scheme 1.9**). So, using established methodolodgy,[28] the ring-fused *gem*-dibromocyclopropane **1.69** was subjected to an electrocyclic ring-opening/nucleophilic trapping sequence that led to the cyclohexenylamine[29] **1.70** in three steps. Suzuki–Miyaura cross-coupling[30] of compound **1.70** with the commercially available aryl boronic acid **1.71** then gave the arylated cyclohexene **1.72** that was treated with sodium hydride then 1-bromo-2-butyne and thus affording the compound **1.73** required for the pivotal IMAE reaction. In the event, subjecting this last compound to reaction with $Pd(OAc)_2$ and the strongly σ-donating and bidentate ligand *N*,*N'*-bis(benzylidene)ethylenediamine (BBEDA) gave the required and previously reported[28] *cis*-C3a-arylhexahydroindole **1.75** in 94% yield. Selective oxidative cleavage of the exocyclic double bond associated with diene **1.75** using potassium osmate(VI) dihydrate and *N*-methylmorpholine *N*-oxide (NMO) in the presence of citric acid and then treatment of the resulting mixture of diastereoisomeric diols with phenylliodonium diacetate gave ketone **1.76** in 38% yield. Simple manipulations of this ketone then provided the aminoalchol **1.77** that was subjected to a Pictet-Spengler reaction and thus affording the racemic modification of the structure, **1.78**, assigned to the natural product heamultine. Given that compounds **1.75**, **1.76**, and **1.77** associated with this reaction sequence all possess the same ACE core as encountered in gracilamine, the adaptation of these protocols to the assembly of this more complex natural product became the major objective of the author's PhD studies.

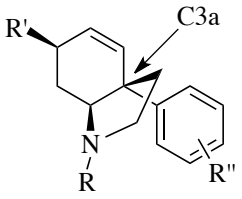


Scheme 1.9: Total Synthesis of Haemultine.

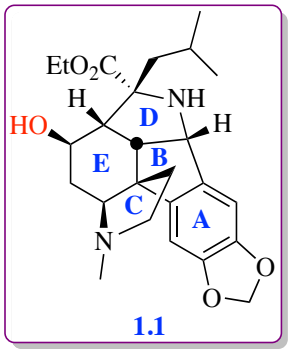
Chapter Two: A Model Study Exploring the Pd-Catalysed IMAE Reaction and Testing the Intramolecular [3+2]Cycloaddition Process

2.1 The Pd-Catalyzed Intramolecular Alder-ene (IMAE) Reaction

Banwell and co-workers[28, 31] have reported, that the Pd(II)-catalyzed intramolecular Alder-ene (IMAE) reaction of propargylated 1-amino-2-aryl-2-cyclohexenes allows for the generation of C3a-arylated hexahydroindoles **1.67** and subsequently deployed this and closely related processes in the synthesis of a range of natural products and natural product scaffolds.[27, 32]



1.67



1.1

The basic reaction pathway associated with the synthesis of C3a-arylated hexahydroindoles *via* such an IMAE process is shown in **Figure 1.6**. In principle, the IMAE reaction may be promoted thermally or by using a transition metal such as palladium (in a lower-valent state).[33] By such means, an *N*-protected and propargylated 1-amino-2-aryl-2-cyclohexene of the general form **2.1** is converted into a *cis*-3a-arylhydroindole **2.2** (corresponding to a protected form of **1.67**) incorporating a Δ^4-double bond as well as an exocyclic one at C-3. Provided the latter alkene can be oxidatively cleaved in a selective manner, this unit should serve as an intermediate in the synthesis of gracilamine (**1.1**). Given the geometrical requirements for the IMAE reaction, (**Figure 1.6**) the nature of the protecting group, P, at the nitrogen in substrate **2.1** is almost certain to be crucial to success. In particular, this

group must allow the nitrogen-based substituents to assume a tetrahedral geometry and, thereby, the alkyne to interact in the necessary fashion with the endocyclic double bond and the associated allylic methylene unit (of the substrate undergoing the IMAE reaction). Based on previous studies by Banwell and co-workers,[28] the tosyl and nosyl moieties were chosen as the preferred protecting groups in the author's work detailed below.

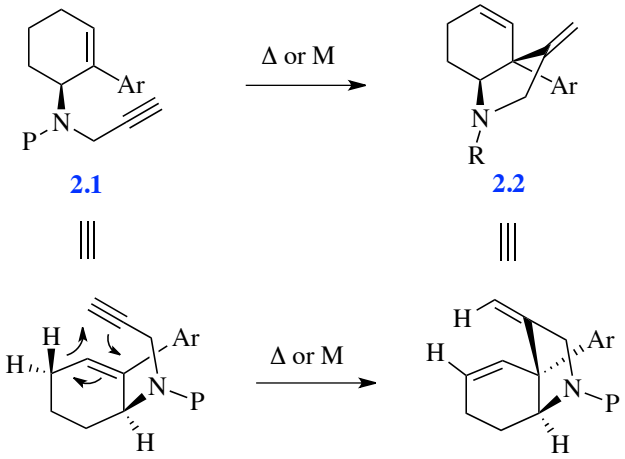
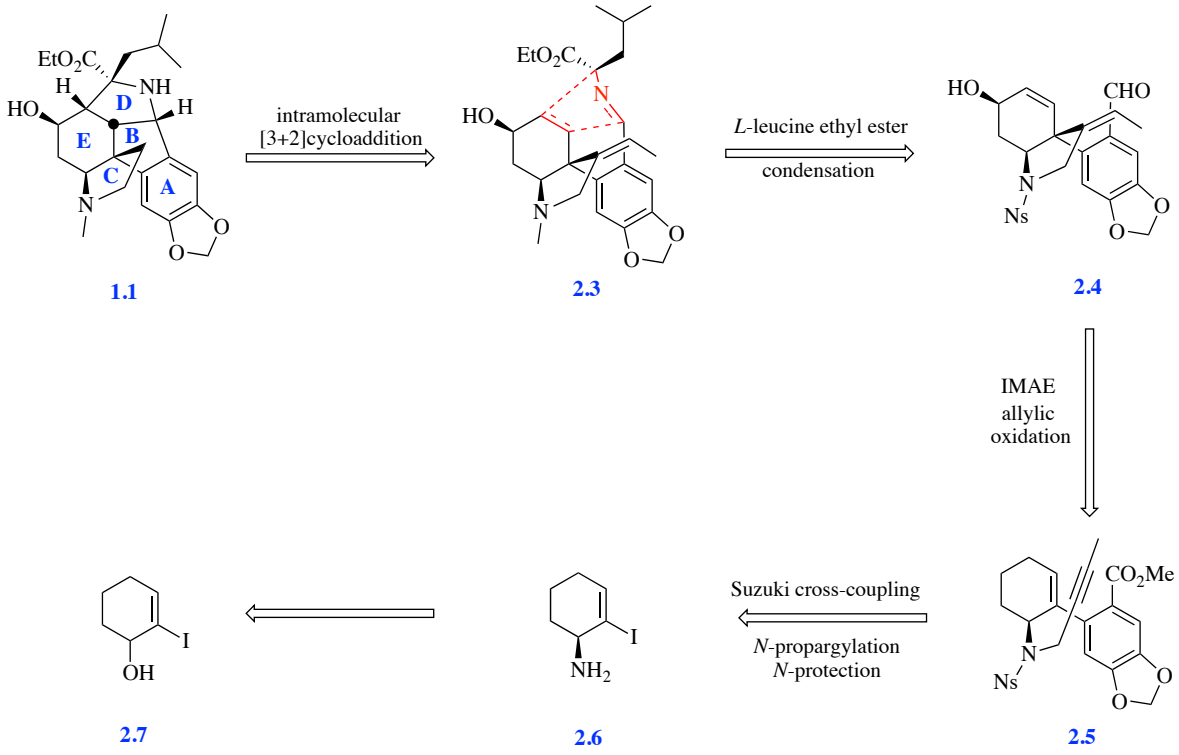


Figure 1.6: Proposed Synthesis of C3a-Arylated Hexahydroindoles via an IMAE Reaction. (M = Pd[0])

2.2 Retrosynthetic Analysis of Gracilamine

A reaction sequence that mimics the proposed[1] biogenesis of the pentacyclic ABCDE-framework of (±)-gracilamine (**1.1**) and that may, in principle, be used to generate this target is shown in **Scheme 1.10**. This involves an intramolecular [3+2]cycloaddition reaction of the unsaturated azomethine ylide **2.3** that might itself be generated through an Schiff-base condensation reaction between the aldehyde **2.4** (containing an embedded C3a-arylated hexahydroindole moiety) and *L*-leucine ethyl ester. Intermediate **2.4** was thought likely to be accessible *via* the previously highlighted IMAE reaction of alkyne **2.5** followed by allylic oxidation. In order to form the IMAE precursor **2.5**, a typical reaction sequence (including Suzuki cross-coupling, *N*-propargylation and *N*-protection steps) developed by Banwell and co-workers[27, 28, 31, 32] was to be followed with the readily available 2-

iodocyclohex-2-en-1-ol (**2.7**) serving as the starting material for the preparation of allylic amine **2.6**. In this retrosynthetic plan, the IMAE and intramolecular [3+2]cycloaddition reactions were considered to be the key steps.



Scheme 1.10: Retrosynthetic Analysis of (±)-Gracilamine (1.1).

2.3 Preparation of a Suitable C3a-Arylated Hexahydroindole

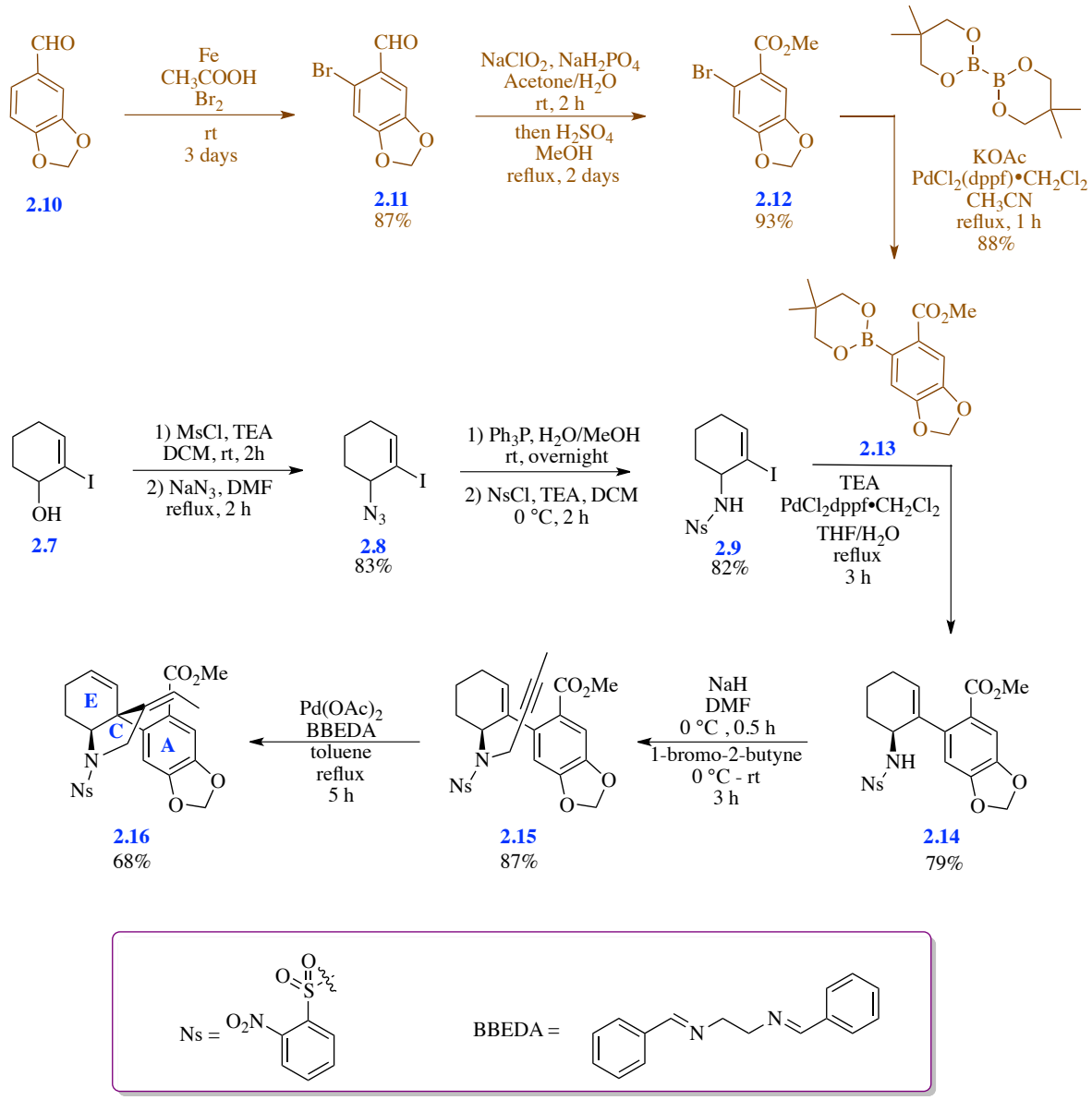
The preparation of a suitable C3a-arylhexahydroindole is shown in **Scheme 1.11** and began with the conversion of the readily available 2-iodocyclohex-2-en-1-ol (**2.7**)[34] into the corresponding mesylate under the Crossland−Servis conditions.[35] The crude ester obtained after aqueous work-up was immediately reacted with sodium azide in *N*,*N*-dimethylformamide at 80 °C to give allylic azide **2.8** in 83% yield. Staudinger reduction of the compound **2.8** with triphenylphosphine in the presence of water and treatment of the

ensuing amine with nosyl chloride (NsCl) then gave sulfonamide **2.9** (82%). The nosyl group was chosen because of the likelihood of the associated nitrogen assuming a geometry that would allow for the desired IMAE to take place and, of course, because of its likely ready removal towards the end of the synthesis.[28]

The cross-coupling partner 6-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzo[*d*][1,3]dioxole-5-carboxylate required for Suzuki-Miyaura cross-coupling with iodide **2.9** was prepared following a previously reported procedure.[36] Thus, and as shown in **Scheme 1.11**, piperonal (**2.10**) was treated with molecular bromine and iron filings in glacial acetic acid and the aryl bromide **2.11**[37] (87%) thereby formed in a regioselective manner. The aldehyde moiety associated with the latter compound was oxidized to the corresponding carboxylic acid using sodium chlorite and this treated with methanol in the presence of sulfuric acid.[38] As a result, the methyl benzoate **2.12** was formed (93%) and upon subjecting this to a Miyaura borylation reaction using bis(neopentylglycolato)diboron in the presence of potassium acetate and catalytic amounts of $PdCl_2(dppf)\bullet CH_2Cl_2$ the required bis-ester **2.13** was obtained in 88% yield.

The cross-coupling of compounds **2.9** and **2.13** under standard Suzuki−Miyaura conditions provided the previously reported[28] and arylated cyclohexene **2.14** in 79% yield. Propargylation at the nitrogen within compound **2.14** was readily achieved by successive treatment of it with sodium hydride then 1-bromo-2-butyne and so producing compound **2.15** (87%),[28] the substrate required for the pivotal IMAE reaction.

With compound **2.15** in hand it was immediately subjected to the conditions used by Trost and Pedregal[39] for effecting IMAE reactions. Specifically, then, it was reacted with $Pd(OAc)_2$ and *N,N'*-bis(benzylidene)ethylenediamine (BBEDA) in refluxing toluene. As a result the hexahydroindole **2.16** was obtained in 68% yield after chromatographic purification.[28]

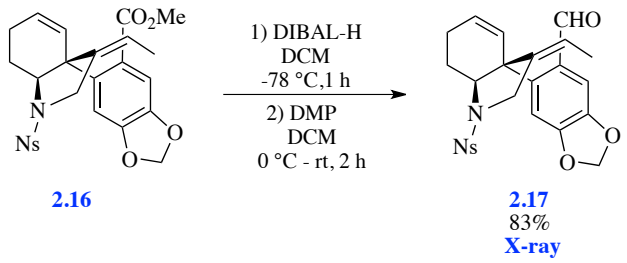


Scheme 1.11: The Synthetic Route Leading to the C3a-Arylated Hexahydroindole 2.16.

2.4 Preparation of the Substrate Required for Examining the [3+2]Cycloaddition Reaction

With the successful assembly of the AEC ring system of gracilamine (as embodied in compound **2.16**), the next step was to prepare of the aldehyde required for participation in Schiff-base condensation reaction and thus providing the substrate necessary for examining the intramolecular and biomimetic [3+2]cycloaddition reaction.

As shown in **Scheme 1.12**, the required manipulation of ester **2.16** so as to generate the corresponding aldehyde was a very straightforward matter. This simply involved exposing a dichloromethane solution of the former compound to DIBAl-H at –78 °C and then oxidizing the product alcohol to aldehyde **2.17** (83%) using the Dess−Martin periodinane (DMP). By such means and over the two steps involved, compound **2.17** was obtained in 83% yield. All of the spectral data acquired for this product were consistent with the assigned structure but this was finally confirmed by a single-crystal X-ray analysis. The derived ORTEP is shown in **Figure 1.7** and other details of this analysis are presented in the Experimental Section (**Chapter 5**).



2.16 **2.17** 83% **X-ray**

Scheme 1.12: Formation of Aldehyde 2.17 via Reduction of Ester 2.16.

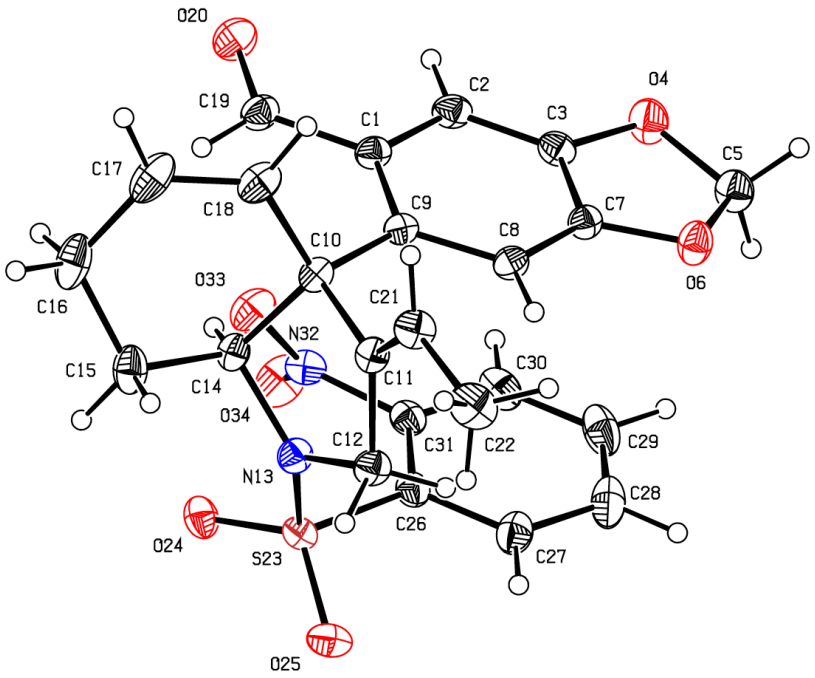
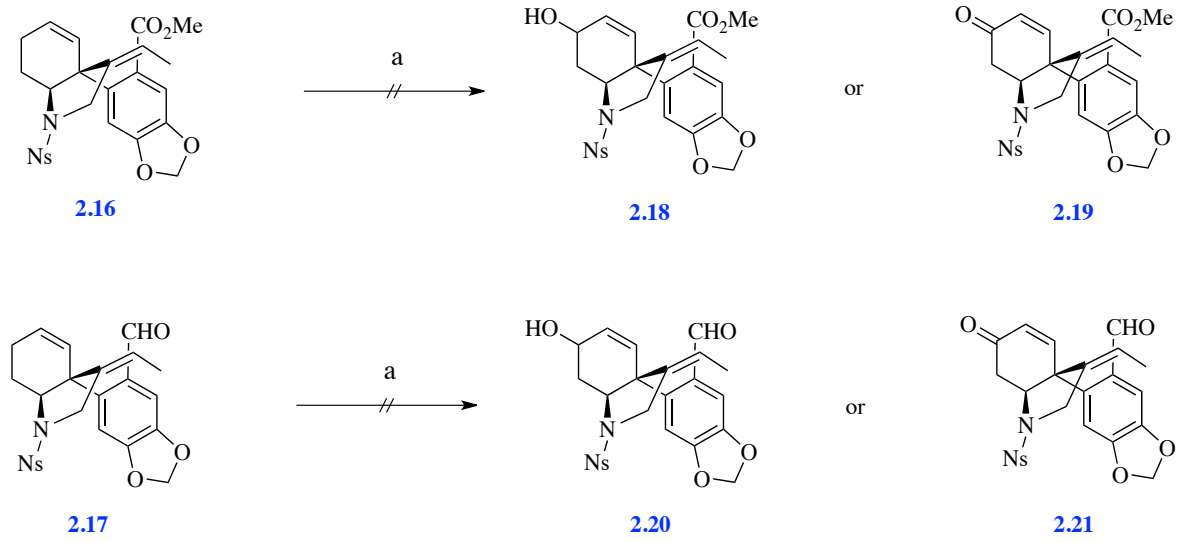


Figure 1.7: ORTEP Derived from the Single-Crystal X-ray Analysis of Compound 2.17.

Given the presence of a hydroxyl group on ring E of gracilamine (**1.1**) efforts were made, at this point, to effect the allylic oxidation of compounds **2.16** and **2.17** using selenium dioxide (**Scheme 1.13**).[40] However, upon exposure of either ester **2.16** or aldehyde **2.17** to the relevant conditions, none of the hoped-for oxidation products **2.18**-**2.21** was observed. Since combinations of manganese triacetate, *tert*-butylhydroperoxide and molecular oxygen have been reported, by Shing *et al,*[41] to effect allylic oxidations, this reagent combination was examined but also to no avail. Decomposition was observed in every instance.



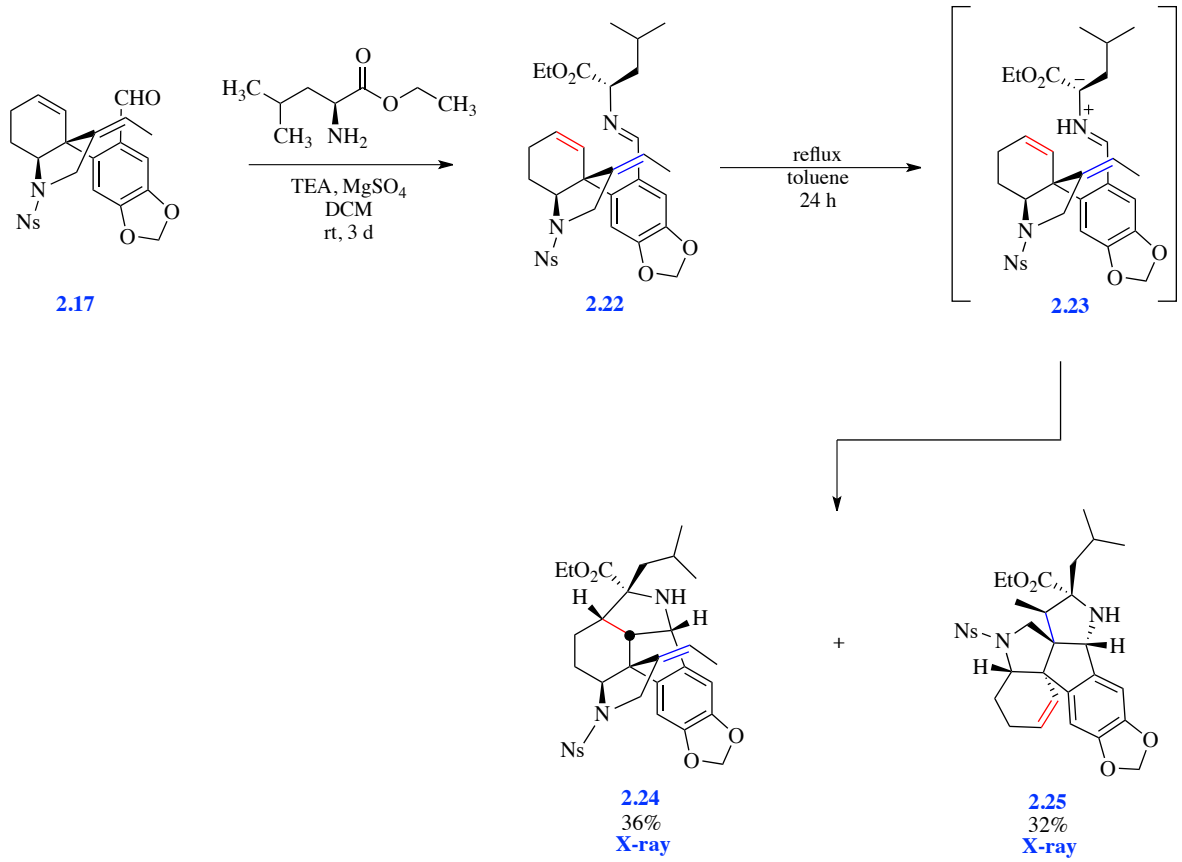
Scheme 1.13: Reagents and Conditions (a) Various Conditions, Including SeO_2; $Mn_3(OAc)_9$,t-BuOOH, O_2.

Despite these failures, compound **2.17** could still be used to study the viability (or otherwise) of the pivotal intramolecular [3+2]cycloaddition reaction. Details of the outcomes of the author's efforts in this area are detailed in the following section.

2.5 Testing the Intramolecular [3 +2]Cycloaddition Reaction

With the substrate **2.17** for the Schiff-base condensation reaction in hand attempts were made to convert it into the ylide required to the title cycloaddition reaction (of course, it was recognized that in carrying this diene-containing substrate forward two such cycloaddition pathways were possible). To such ends, aldehyde **2.17** (**Scheme 1.14**) was treated with ethyl *L*-leucinate in the presence of triethylamine and magnesium sulfate at ambient temperatures for 3 days. The ensuing imine **2.22** was isolated, then immediately subjected to thermolysis in refluxing toluene. The ylide **2.23** so-formed (as a result of a 1,2-prototropic shift) participated in the formation of two chromatographically separable and crystalline [3 + 2]cycloadducts, namely compounds **2.24** (36%) and **2.25** (32%). Each of these was fully characterized using the usual range of spectroscopic methods but final

support for the illustrated structures followed from single-crystal X-ray analyses of each of them. The resulting ORTEPs are presented in **Figures 1.8** and **1.9**.



Scheme 1.14: Testing the Pivotal Intramolecular [3+2]Cycloaddition Reaction.

In both of the products, two rings and four stereocenters were generated. Compound **2.24** is formed as a consequence of azomethine ylide addition onto the endocyclic double bond and so resulting in the assembly of the full complement of rings associated with gracilamine (**1.1**) and which are annulated to one another in the required manner. On the other hand, compound **2.25** clearly arises from azomethine ylide addition onto the exocyclic double bond of the substrate. Given that the yields of these two adducts are very similar it is clear that there is very little difference in the transition state energies associated with the reaction pathways leading to these two cycloadducts.

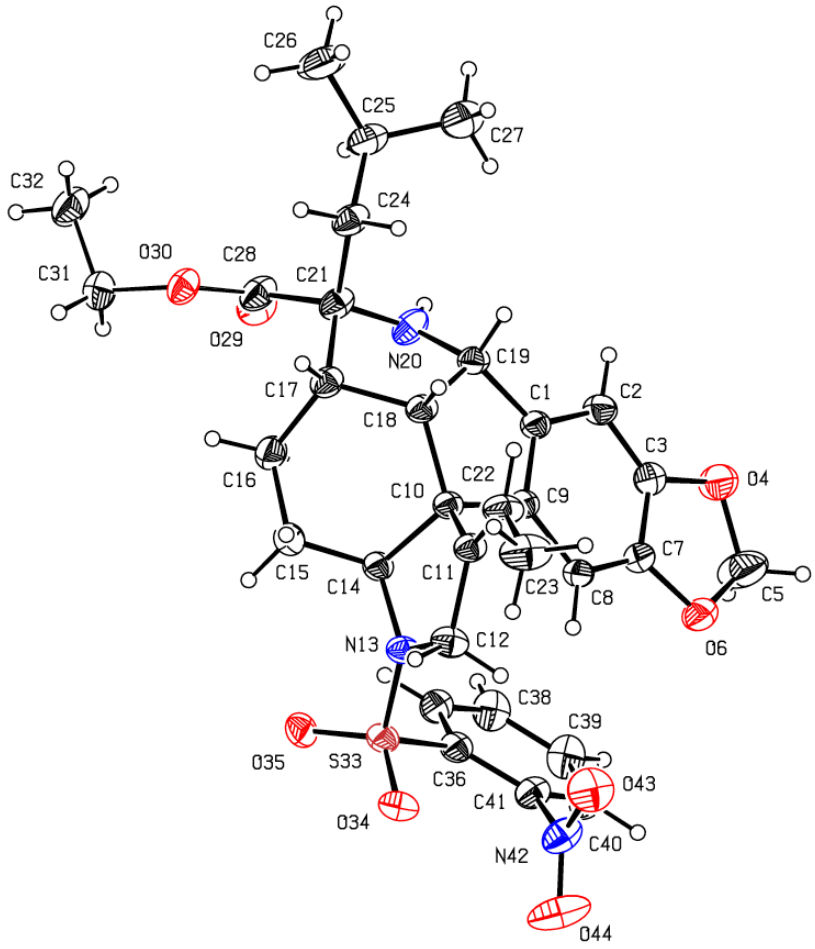


Figure 1.8: ORTEP Derived from the Single-Crystal X-ray Analysis of Compound 2.24.

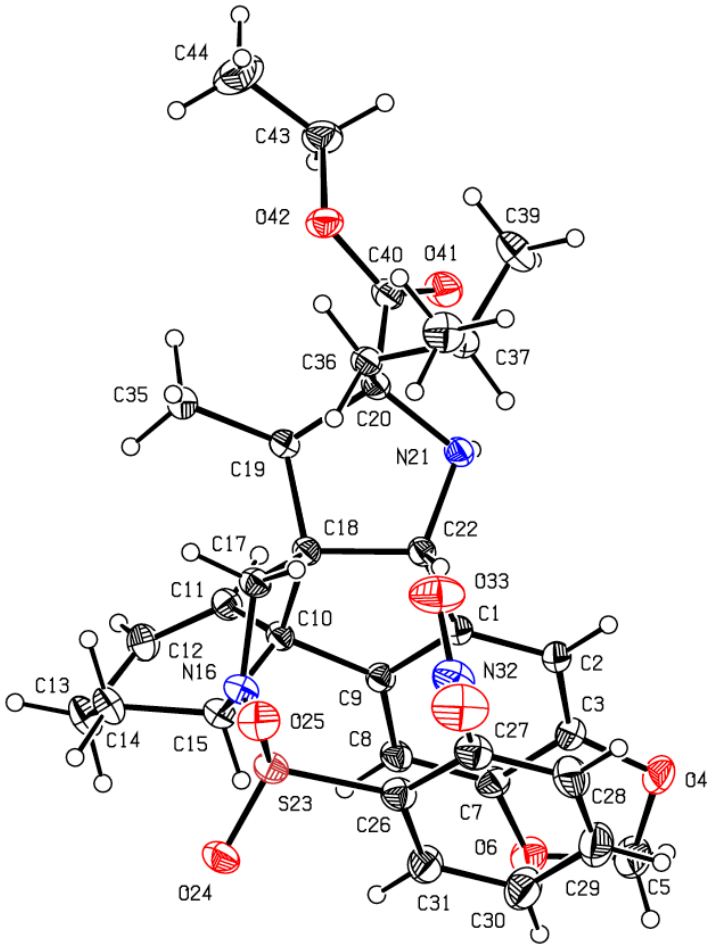


Figure 1.9: ORTEP Derived from the Single-Crystal X-ray Analysis of Compound 2.25.

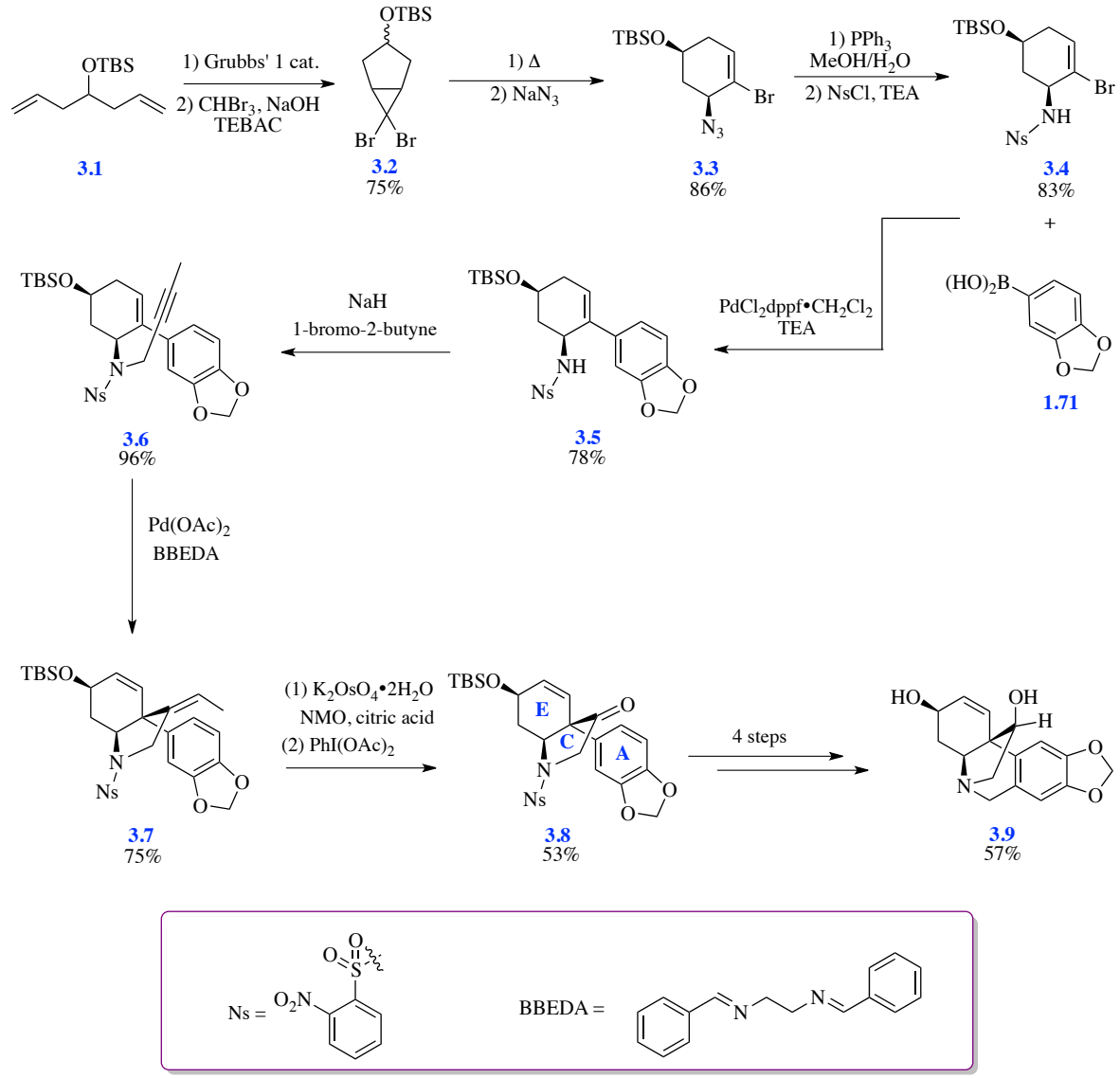
The presence of an exocyclic double bond within C3a-arylated hexahydroindoles prepared by the route just described is an inevitable consequence of the use of the IMAE reaction to prepare such systems,[28, 31] and the model study clearly indicates that it participates in [3 + 2]cycloaddition reactions when the ylide is appended to the C3a aryl unit. Based on such observations, the excision of this group, as well as the introduction of the E-ring hydroxyl group of gracilamine (**1.1**) became the major concerns associated with the campaign leading to this target alkaloid. Details of the relevant studies are presented in the following chapters.

Chapter Three: Initial Studies on the "Real" System and the Challenges So Revealed

3.1 Relevant Previous Studies

One aspect of the work described in the preceding chapter was the failure to install the hydroxyl group associated with the E-ring of gracilamine at a late stage in the reaction sequence. This chapter details studies on the alternate ways investigated by the author in her efforts to complete a synthesis of gracilamine. The basic approach involved incorporating the hydroxyl functional group from the very beginning of the synthesis. Such an approach was inspired by the total synthesis of hamayne reported in 2011 by Banwell and co-workers[32a] (**Scheme 1.15**). In this work, they started with the known[42] and readily obtained *tert*-butyldimethylsilyl (TBS) ether **3.1**, this compound being subjected to a ring-closing metathesis (RCM) reaction[43] using Grubbs' first-generation catalyst.[44] The ensuing cyclopentene was reacted with dibromocarbene generated under the Makosza conditions[45] from bromoform and sodium hydroxide in the presence of the phase-transfer catalyst triethylbenzylammonium chloride (TEBAC). As a result a *ca*. 5:1 mixture of two diastereoisomeric cyclopropanes of the general form **3.2** was produced with the major one being readily obtained in 75% yield after flash chromatography. Compound **3.2** was subjected to thermally induced electrocyclic ring-opening in refluxing chlorobenzene and upon treatment of the ensuing 2,3-dibromocyclohexane with sodium azide in *N*,*N*-dimethylformamide the allylic azide **3.3** was obtained in 86% yield with *ca*. 6% of the corresponding and chromatographically inseparable *trans*-isomer accompanying it. Azide **3.3** was treated with triphenylphosphine in methanol/water and the resulting primary amine reacted with nosyl chloride to give the sulfonamide **3.4** in 83% yield. Suzuki-Miyaura cross-coupling of compound **3.4** with commercially available boronic acid **1.71** then gave the arylated cyclohexane **3.5** (78%) that was *N*-propargylated using 1-bromo-2-butyne in the presence of sodium hydride. This produced, in 96% yield, the substrate, **3.6**, required for the pivotal IMAE reaction. In the event, microwave irradiation of a benzene solution of alkyne **3.6** containing $Pd(OAc)_2$ and BBEDA afforded, *via* the anticipated IMAE process, the cyclisation product **3.7** and selective reaction of this product under Upjohn conditions[46]

resulted in regioselective dihydroxylation of the more substituted double bond within diene **3.7**. Treatment of the ensuing diols with phenyliodonium diacetate in dichloromethane then gave ketone **3.8** in 53% yield. Subsequent deprotection, reduction and Pictet-Spengler cyclisation reactions followed by a saponification then delivered hamayne (**3.9**) in 57% overall yield.

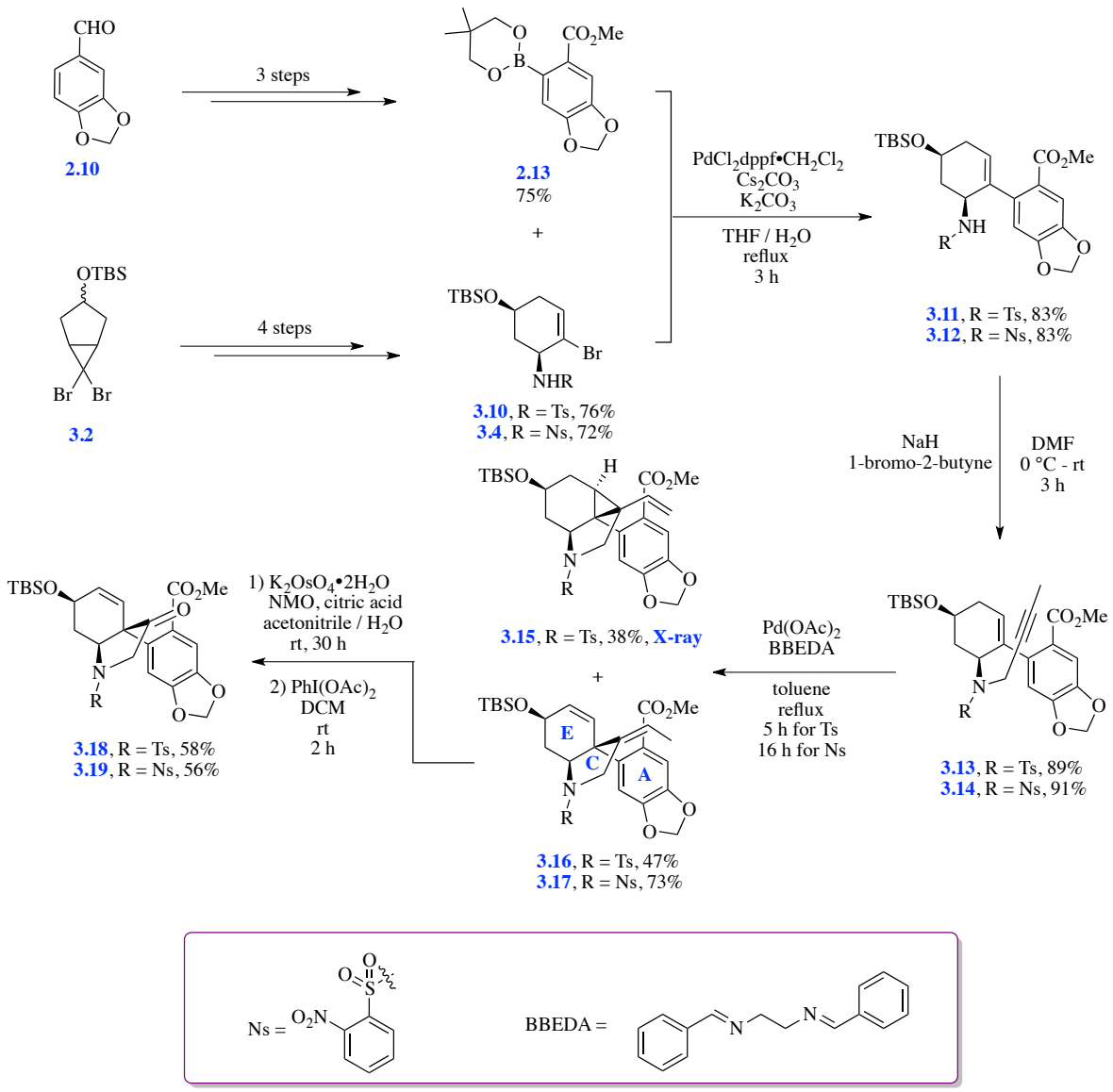


***Scheme 1.15: Total Synthesis of Hamayne by Banwell* et al.**

3.2 Extensions, by the Author, of the Approach to Hamayne to the Synthesis of Gracilamine

The synthesis of a C3a-arylhexahydroindole carrying an E-ring hydroxyl group and potentially suitable for elaboration to gracilamine is shown in **Scheme 1.16**. Thus, the previously reported[32a)] 6,6-dibromobicyclo[3.1.0]hexan-3-ol derivative **3.2** was converted, by established methods, into the Ts-*N*-protected or Ns-*N*-protected allylic amines **3.10** (76%) and **3.4** (72%), respectively. Suzuki−Miyaura cross coupling of these last compounds with boronate ester **2.13**[36] then gave the corresponding arylated cyclohexene **3.11** and **3.12**, and these, in turn, were engaged in an *N*-propargylation reaction of the same type as used in the model study. By such means the *N*-linked 1,6-enynes **3.13** (89%) and **3.14** (91%), respectively, were obtained.

Compounds **3.13** and **3.14** were engaged, separately, in the required IMAE reaction using $Pd(OAc)_2$ and BBEDA in refluxing toluene. When the nosyl-protected analogue **3.14** was reacted under these conditions, the *cis*-3a-arylhydroindole **3.17** was obtained in 73% and this was accompanied by small amounts of uncharacterised material. A less satisfying outcome involved the tosyl-protected analogue **3.13** as substrate and with the desired C3a-arylhexahydroindole **3.16** now being obtained in just 47% yield under the same conditions. This was because it was accompanied by its cyclopropane-annulated isomer **3.15** (38%), the structure of which was confirmed by single-crystal X-ray analysis (**Figure 1.10**).



Scheme 1.16: Synthesis of the C3a-Arylhexahydroindole Bearing an E-Ring Hydroxyl Group.

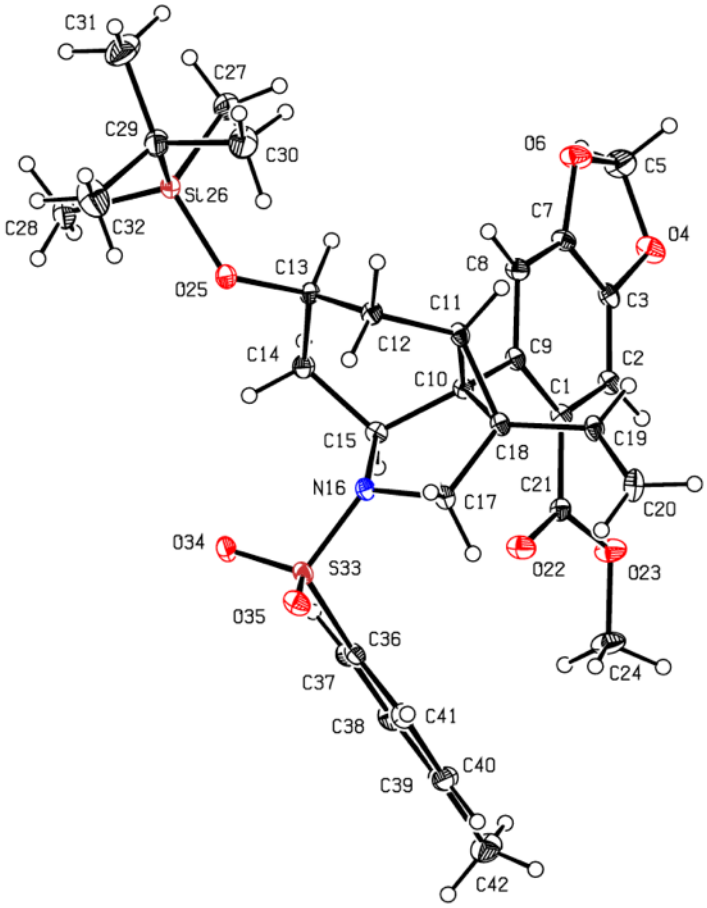


Figure 1.10: ORTEP Derived from the Single-Crystal X-ray Analysis of Compound 3.15.

Presumably, the cyclopropane-annulated hexahydroindole **3.15** arises through participation of the initially formed (and desired) *cis*-3a-arylhydroindole in a secondary IMAE reaction involving the ethylidene and endocyclic alkene units. Attempts to suppress this secondary process by using milder reaction conditions have, thus far, been ineffective.

Compounds **3.16** and **3.17** closely resemble the *cis*-3a-arylhydroindole unit discussed in previous chapter, differing only in that they incorporate a TBS ether in ring E. Importantly, this ether group is configured correctly for elaboration to gracilamine. Since the TBS ether is an electron-withdrawing group it was expected to deactivate the nearby cyclohexene double bond toward electrophilic attack. Moreover, the bulkiness of this ether should also provide a steric impediment to such attack. As a result, reasonably selective dihydroxylation reactions were observed upon treating these compounds with potassium

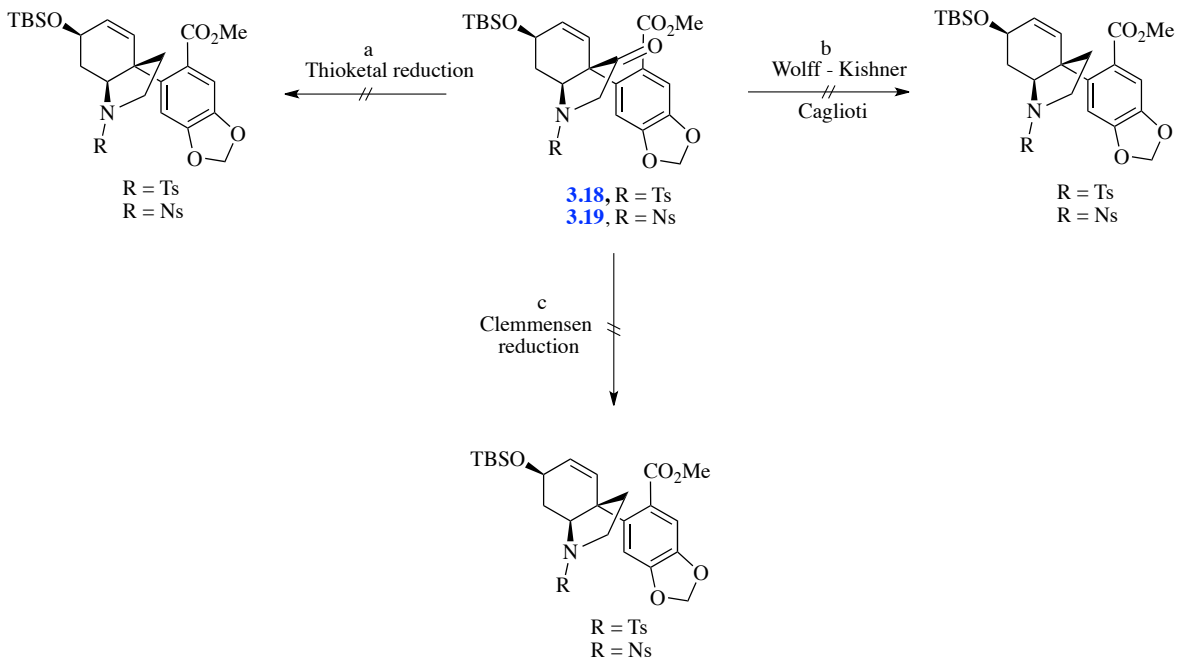
osmate(VI) dihydrate and *N*-methylmorpholine *N*-oxide in presence of citric acid. Oxidative cleavage of the corresponding diols using iodobenzene diacetate[47] then gave ketones **3.18** (58%) and **3.19** (56%), respectively.

Since the exocyclic double bond could be selectively removed using oxidative cleavage protocols, complete deletion of the ketone group within compounds **3.18** or **3.19** was now necessary in order to complete the total synthesis of gracilamine. Efforts towards such ends are detailed in the following section.

3.3 Attempts to Deoxygenate Ketones 3.18 and 3.19

3.3.1 A Two-step Approach

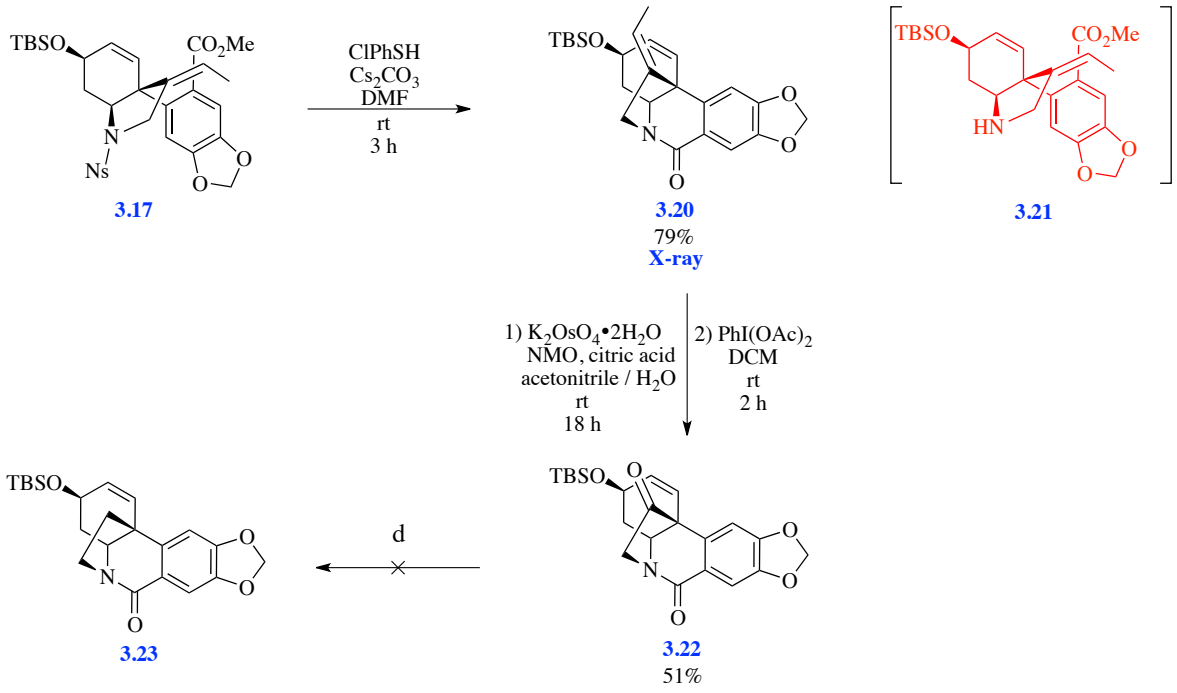
In the author's first attempt to remove the ketone residues within the polyfunctionalised compounds **3.18** and **3.19** protocols involving mild reaction conditions were sought. As such, ones involving thioketal intermediates were investigated.[48] Two different forms of these, namely 1,3-dithiane and 1,3-dithiolanes were studied first. However, despite investigating a range of different reaction conditions, neither of these derivatives could be formed. Subjecting compounds **3.18** and **3.19** to Wolff-Kishner reduction conditions,[49, 50] (requiring highly basic conditions) or a Clemmensen reduction (involving the use of acidic conditions)[51] also failed to deliver any useful outcomes (**Scheme 1.17**).



Scheme 1.17: Summary of the Various Attempts Made to De-Oxygenate Ketones 3.18 and 3.19.

3.3.2 Removing the Sulfonyl-Protecting Group before Deoxygenation

On the basis that the presence of the sulfonamide residues within compounds **3.18** and **3.19** might be adversely affecting the attempted deoxygenation processes (as described immediately above) efforts were made to remove these. Accordingly, and as shown in **Scheme 1.18**, compound **3.17** was treated with *p*-chlorobenzenethiol and cesium carbonate in *N*,*N*-dimethylformamide at ambient temperatures, conditions defined by Fukuyama for the cleavage of nosylates.[52] In the present case, however, this not only resulted in removal of the sulfonamide residue (presumably leading to intermediate **3.21**) but also in a (subsequent) lactamisation reaction involving the pendant ester residue and thus affording compound **3.20** (79%), the structure of which was confirmed by single-crystal X-ray analysis. (**Figure 1.11**)



Scheme 1.18: Manipulation of Compound 3.17 Leading to Lactams 3.20 and 3.22.

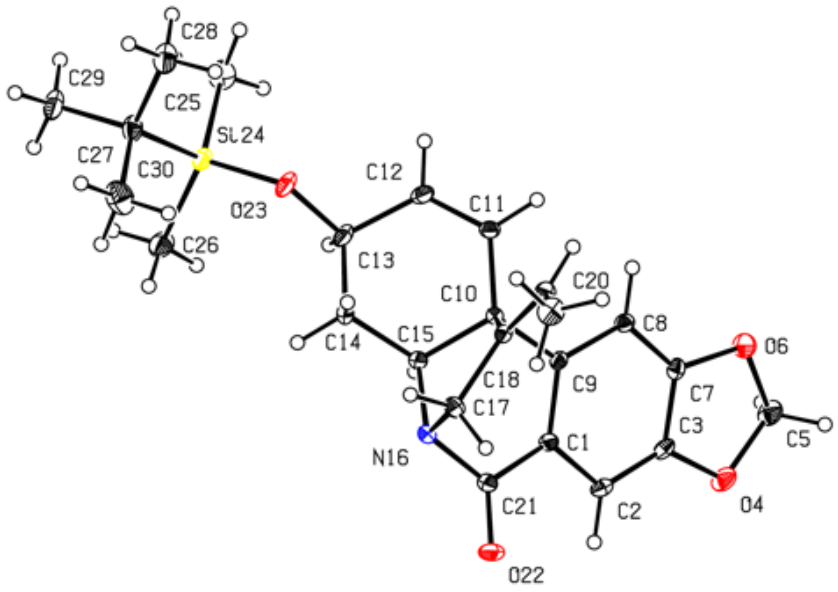
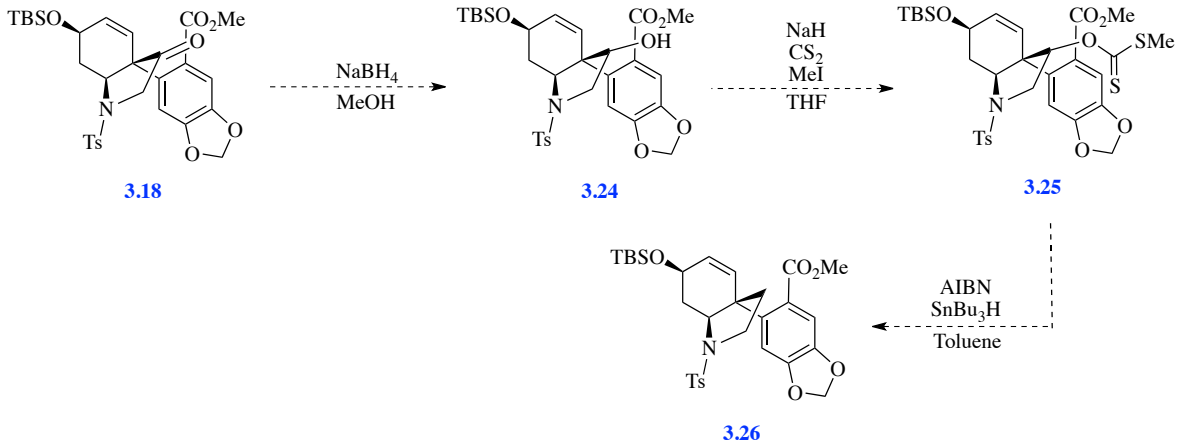


Figure 1.11: ORTEP Derived from the Single-Crystal X-ray Analysis of Compound 3.20.

Compound **3.20** was subjected to oxidative cleavage of its exocyclic double bond through a selective dihydroxylation reaction employing the conditions mentioned earlier and involving potassium osmate (VI) dihydrate and *N*-methylmorpholine *N*-oxide in presence of citric acid. The *cis*-vicinal diol so-formed was itself treated with iodosobenzene diacetate and by such means ketone **3.22** was obtained in 51% yield over the two steps involved. Further to the commentary provided above, the Wolff-Kishner, thioketal formation/cleavage and Clemmensen reduction protocols were applied to compound **3.22**. Unfortunately, in each instance no recognizable product was obtained.

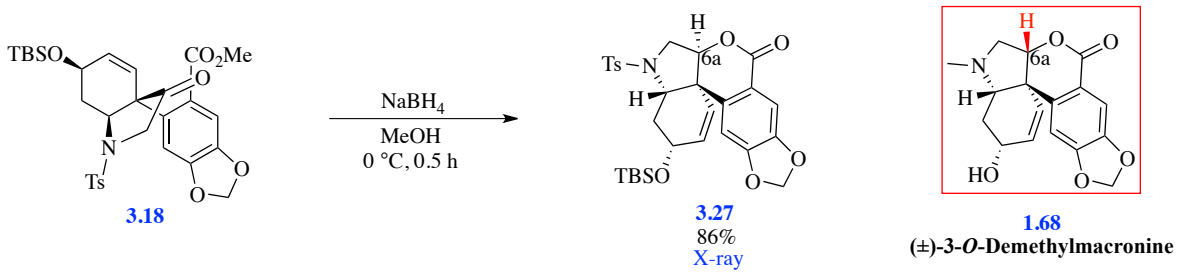
3.3.3 A Three-step Approach

Given the difficulties encountered in the removing the ketone residue using two-step protocols as detailed above, a three-step, Barton-McCombie-based deoxygenation protocol was investigated as outlined in **Scheme 1.19**. Thus, it was expected that if ketone **3.18** were reduced to the corresponding alcohol **3.24** then this could, in turn, be converted into the corresponding methyl xanthate **3.25**. Barton-McCombie deoxygenation of this last compound using tri-*n*-butyltin hydride would then be expected to afford target compound **3.26**.



Scheme 1.19: A Possible Three-step Means of Deoxygenating Ketone 3.18 and Leading to Compound 3.26.

In the event, upon treating compound **3.18** with sodium borohydride in methanol (**Scheme 1.20**) the ketone carbonyl moiety was reduced in a stereoselective manner but the alcohol so-formed reacted with the pendant methyl ester residue to form lactone **3.27** in 86% yield. The structure of this product was initially established using the usual range of spectroscopic techniques but finally confirmed by single-crystal X-ray analysis (**Figure 1.40**). Since the tetracyclic framework of compound **3.27** is related to that seen in the natural product 3-*O*-demethylmacronine (**1.68**). As such this alkaloid was targeted for synthesis as detailed below.



Scheme 1.20: The Reductive Conversion of Ketone 3.18 into Lactone 3.27 and the Resemblance of the Latter to the Alkaloid 3-O-Demethylmacronine (1.68).

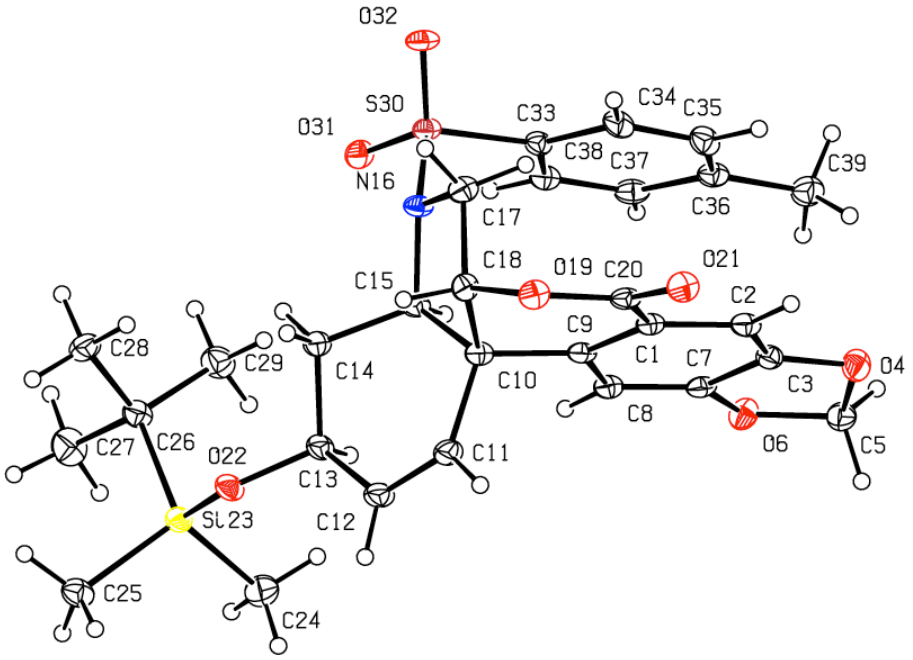
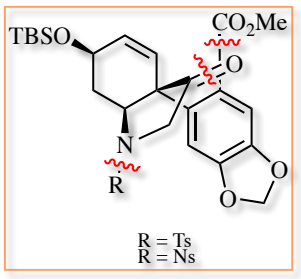


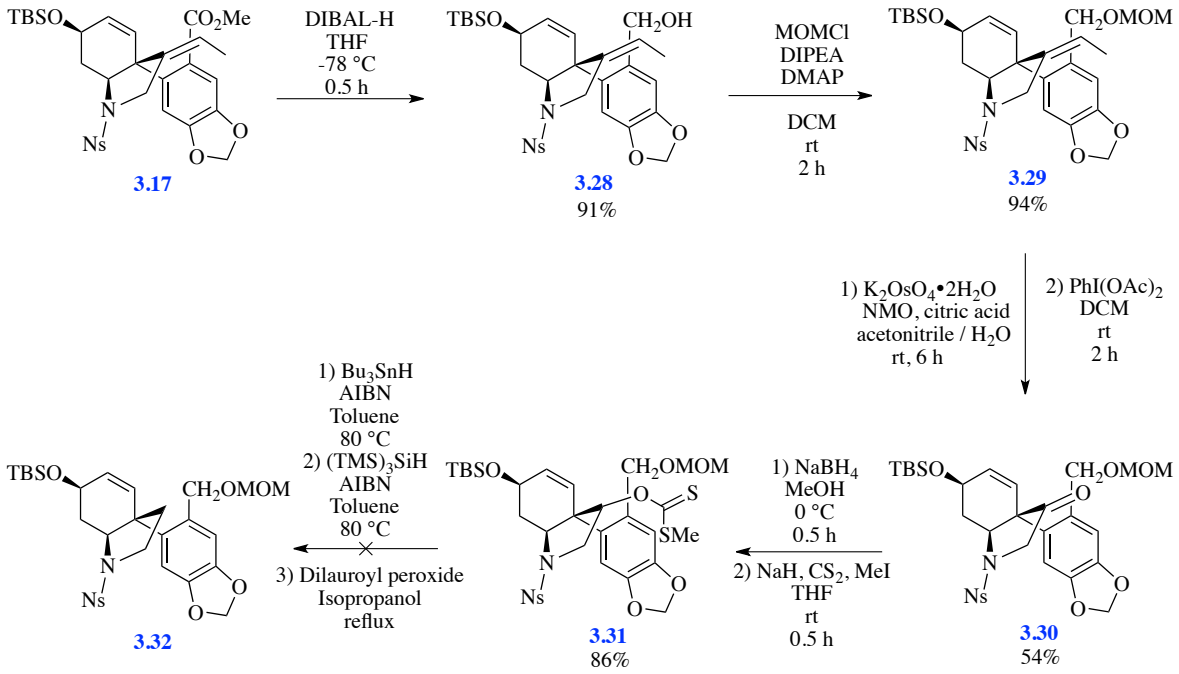
Figure 1.12: ORTEP Derived from the Single-Crystal X-ray Analysis of Compound 3.27.

3.3.4 Masking the Ester Moiety before Conducting the Barton-McCombie Deoxygenation Reaction



As described above, the alcohol and amine groups derived from reduction or deprotection of compounds **3.18** and **3.17** have a high propensity to interact with the pendant ester moiety. In order to prevent such processes from interfering with the desired deoxygenation process, ester **3.17** was reduced (**Scheme 1.21**), using DIBAl-H, to the corresponding alcohol **3.28** and this was immediately protected, through reaction with chloromethyl methyl ether, as the MOM ether (94%). Oxidative cleavage of the exocyclic double bond

associated with the methoxymethyl ether **3.29** under the same Upjohn dihydroxylation conditions[46] and then treatment of the resulting diols with iodobenzene diacetate afforded ketone **3.30** in 54% yield. Product ketone **3.30** was then reduced, in a stereoselective manner, to the corresponding alcohol using sodium borohydride in methanol, and this was itself converted into the methyl xanthate **3.31** (86%). However, subjection of this last compound to Barton−McCombie deoxygenation under a range of different conditions failed to generate the hoped-for compound **3.32**.



Scheme 1.21: A Further Attempt to Remove the Exocyclic Olefin Moiety Associated with Compound 3.17.

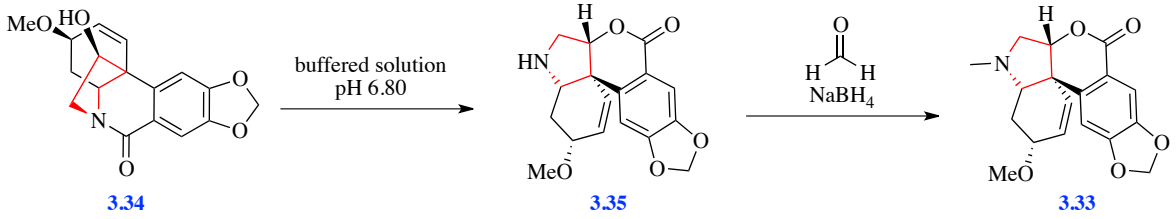
Given the failures detailed above and in order to derive some benefit from the extensive efforts of the author in this area, attention turned to exploiting the lactonisation process just described in developing a synthesis of the macronine type alkaloids including compound **3.22**.

3.4 Previous Synthetic Studies on the Macronine-type Alkaloids

In 1964, Hauth and Stauffacher reported[53] the isolation of the alkaloid macronine (**3.33**) (**Figure 1.13**) from the plant *Crinum macrantherum* Engl. (*Amaryllidaceae*). The assignment of its full structure, by Wildman and co-workers,[54] followed shortly thereafter. The latter group noted that compound **3.33** represents the first example of a lactonic *Amaryllidaceae* alkaloid possessing the tazettine ring system.

Figure 1.13: Structures of the Alkaloid Macronine (3.33) and Its 3-O-Demethylcongener (1.68).

They also revealed that the strained lactam **3.34** **(Scheme 1.22)** incorporated within the haemanthidine alkaloid framework rearranges to give *N*-demethylmacronine **3.35** in aqueous buffer at pH 6.80 and that the latter compound undergoes reductive methylation, in the presence of formaldehyde and sodium borohydride, to give alkaloid **3.33**. Whether or not rearrangements such as **3.34** → **3.35** have biosynthetic relevance remains unclear.

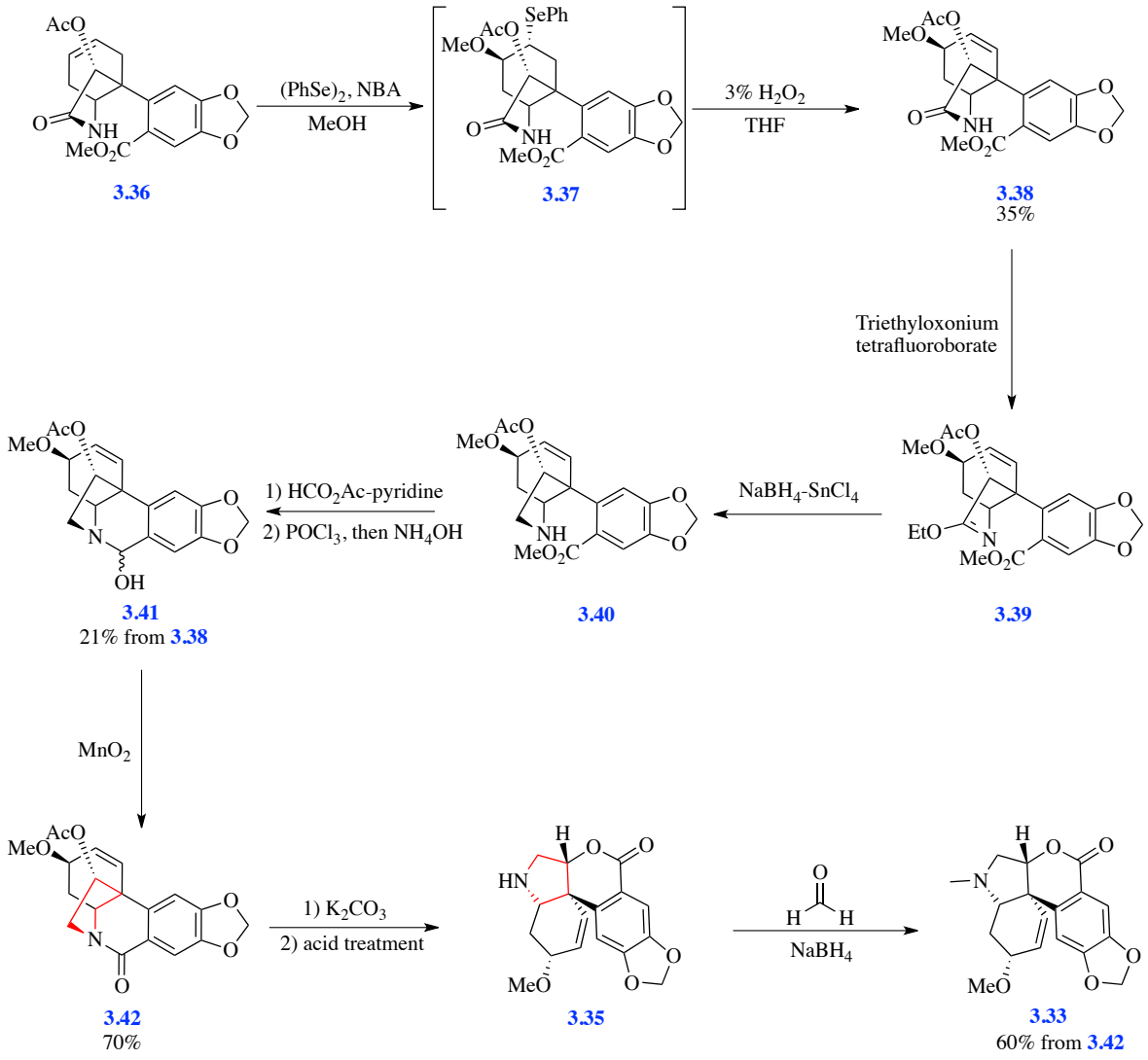


Scheme 1.22: Literature Transformation Leading to Macronine (3.33).

In 1999, Hesse and co-workers[55] described the isolation of 3-*O*-demethylmacronine (**1.68**) from a *Galanthus* species of plants of Turkish origin and the illustrated structure was established using conventional NMR spectroscopic methods. The same group also determined that the compound does not arise through demethylation of congener **3.33** during the isolation process. Accordingly, 3-*O*-demethylmacronine (**1.68**) is considered to be a naturally occurring alkaloid.

Thus far, no biological evaluation of compound **1.68** has been reported. Furthermore, while macronine (**3.33**) has been isolated from a range of plant sources since 1964,[56] studies of its potential therapeutic properties appear to have been confined to ones utilising crude extracts of the producing plants and thus suggesting that it may possess, at a minimum, useful antibacterial and/or antifungal properties.[56 d,e)]

In 1976, Tsuda *et al*.[57] reported a *ca*. 14-step synthesis of (±)-macronine (**Scheme 1.23**) that exploited, as a late-stage transformation, a rearrangement reaction of the type described by Wildman. Thus, treatment of compound **3.36** with $(PhSe)_2$ and *N*-bromoacetamide[58] in methanol followed by oxidation of the resulting methoxy-selenide **3.37** with 3% H_2O_2 in tetrahydrofuran gave, after thermally-induced elimination of the phenylselenoxide so-formed, the allyl methyl ether **3.38**. This last compound was converted into the imino-ether **3.39** on treatment with triethyloxonium tetrafluoroborate and reduction of this with sodium borohydride /$SnCl_4$•$2Et_2O$ complex[59] gave the free amine **3.40** that was formylated using the mixed anhydride HCOOAc in the presence of pyridine and the resulting formamide treated with $POCl_3$. Basification of the ensuing reaction mixture with dilute NH_4OH then gave the cyclized product **3.41**. Oxidation of compound **3.41** with manganese dioxide produced the corresponding lactam **3.42** and after hydrolysis with K_2CO_3, the free hydroxyl group was revealed and thus triggering the rearrangement reaction described above and producing, after acidic work-up, lactone **3.35**. Reductive methylation of this last compound under standard conditions then gave the natural product **3.32** (60% from **3.42**).



Scheme 1.23: The Synthesis of Macronine by Tsuda and Co-workers.

No other relevant work on alkaloids **1.68** or **3.33** has been reported in the intervening period and nor do there appear to have been any studies on the stereochemical requirements (if any) of this pivotal and potentially versatile rearrangement process. In addition to developing a novel synthesis of this natural product, it was also the aim of the author's work to undertake a detailed study of the rearrangement reaction.

3.5 Total Synthesis of 3-*O*-Demethylmacronine

3.5.1 Attempting to Selectively Reduce the Ketone 3.18

As detailed above, lactone **3.27** was formed after reducing ketone **3.18** with sodium borohydride. Product **3.27** possesses the same skeletal framework as macronine type alkaloids **1.12** and **3.33**. The main difference between compound **3.27** and the target alkaloids is the opposing stereochemistry at C6a. Accordingly, the first requirement associated with any successful total synthesis of 3-*O*-demethylmacronine (**1.68**) is the need to establish the necessary C6a stereochemistry and efforts to do so involved subjecting ketone to reaction with a range of reducing reagents as shown in. **Figure 1.24**.

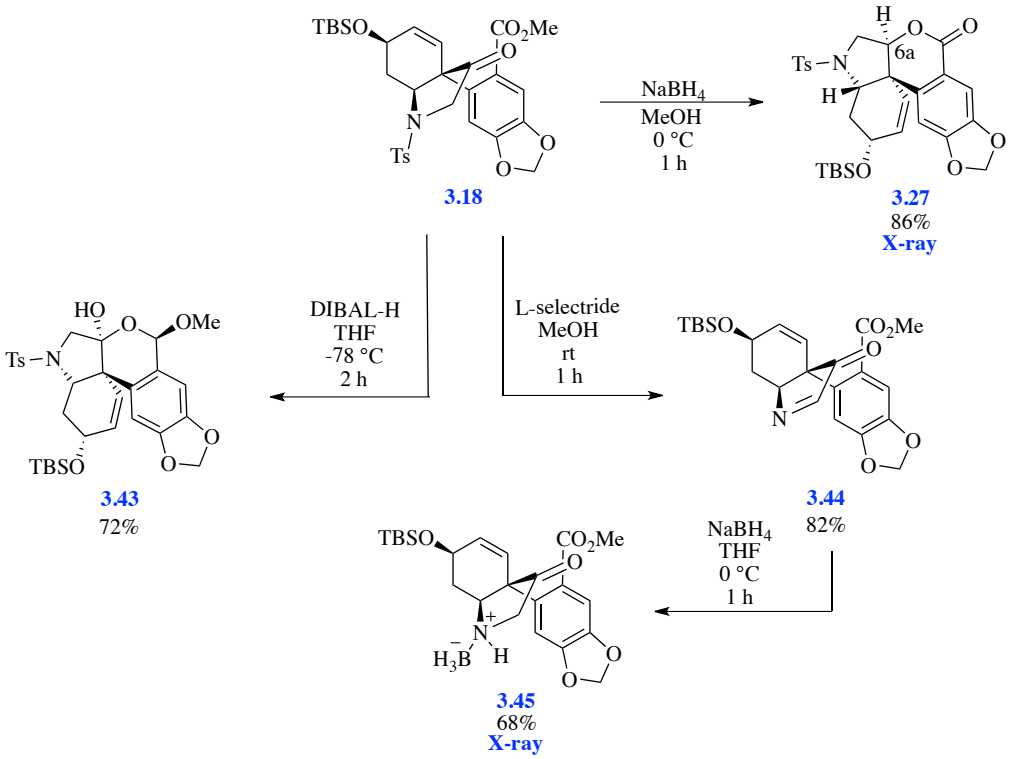


Figure 1.24 : Outcomes of Treating Ketone 3.18 with Different Reducing Reagents.

When compound **3.18** was treated with a bulky reducing agent such as DIBAl-H, in tetrahydrofuran, hydride was added to the ester first and the oxyanion produced as the result of the hydride addition cyclized onto the adjacent carbonyl and the net result was the formation of compound **3.43** in 72% yield. In contrast, when compound **3.18** was treated with L-selectride in methanol then the acyl imine **3.44** was obtained as a result of an $E1_{cb}$ reaction. Reduction of compound **3.44** was also investigated using sodium borohydride but this only resulted in the formation of the corresponding amine, the structure of which was confirmed through X-ray analysis of the corresponding and readily derived borane adduct **3.45** (**Figure 1.14**).

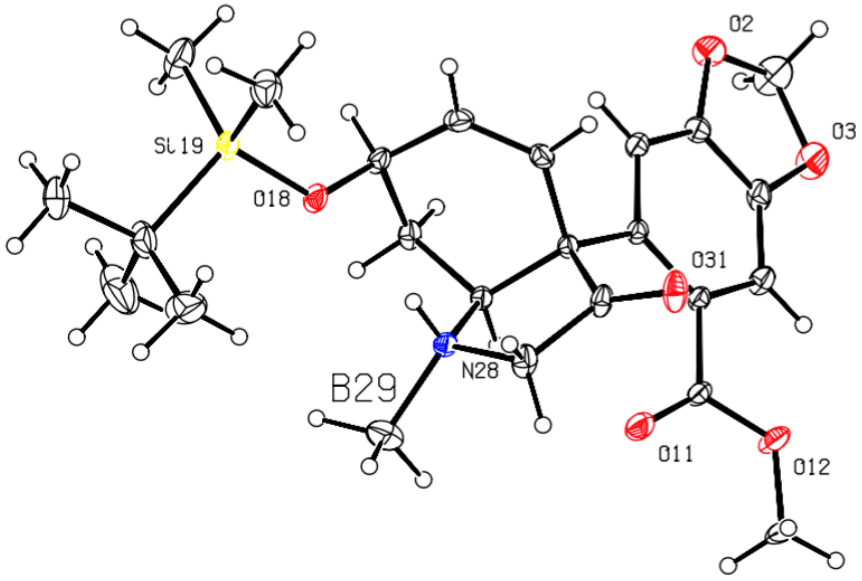
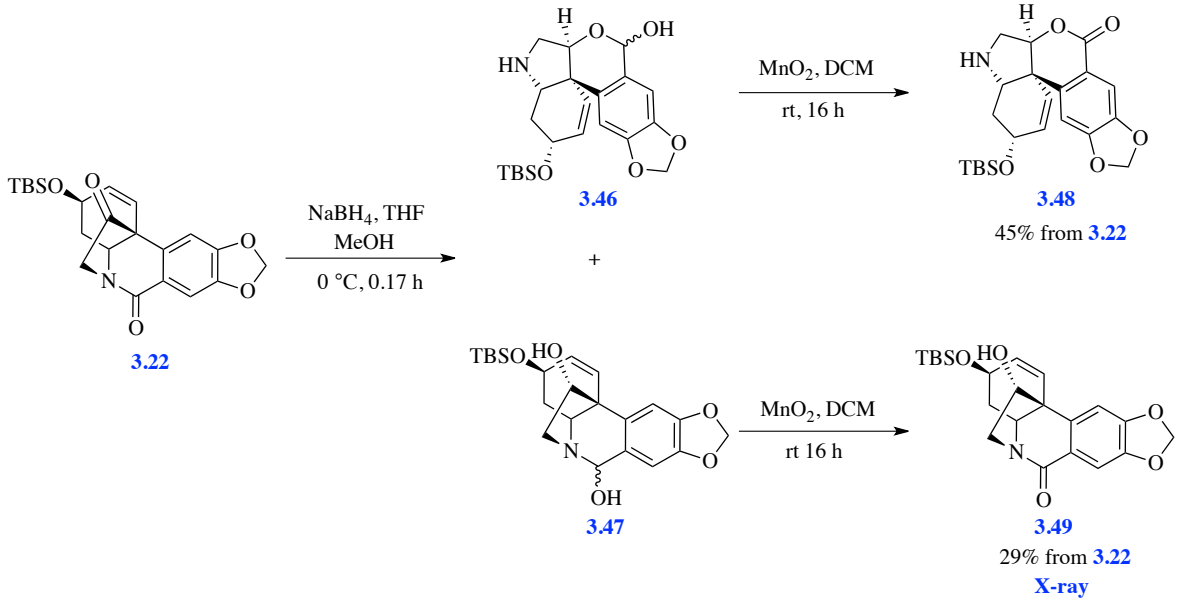


Figure 1.14: ORTEP Derived from the Single-Crystal X-ray Analysis of Compound 3.45.

3.5.2 An Alternate Approach Involving Reduction of the Keto-Lactam 3.22

Another possible approach to solving the C6a stereochemistry "problem" described above would be to effect the stereocontrolled reduction of the keto-lactam **3.22**. This compound displays a lactam carbonyl absorption band at 1700 cm^{-1} in the infrared spectrum, while, in the ^{13}C NMR spectrum of this same material, the associated carbon resonates at δ 179.8

ppm. These values stand as testimony to the strained nature of this nitrogen-containing ring system (the equivalent values for δ-valerolactam are *ca*. 1672 cm^{-1} and δ 169.1ppm, respectively[60]) and as such the correctly configured alcohol derivative would appear to be primed to engage in the lactam to lactone rearrangement leading to the macronine framework. In the event, when a methanolic solution of compound **3.22** maintained at 0 °C was treated with sodium borohydride, non-stereoselective reduction of the associated ketone residue took place to afford a chromatographically separable mixture of compounds **3.46** and **3.47** (**Scheme 1.25**). Since each of these reduction products was obtained as an interconverting mixture of epimers/anomers, they were subjected, as a mixture and without extensive spectroscopic characterisation, to oxidation with manganese dioxide and thereby affording the chromatographically separable lactone **3.48** (45% from **3.22**) and lactam **3.49** (29% from **3.22**), respectively. The structure of the latter product was confirmed by single-crystal X-ray analysis[ii]. (**Figure 1.15**)



Scheme 1.25: Chemical Manipulation of Compound 3.22 Leading to Lactone 3.48 and Lactam 3.49.

[ii] The X-ray structure of compound **3.49** was proved by Mr Xiang Ma

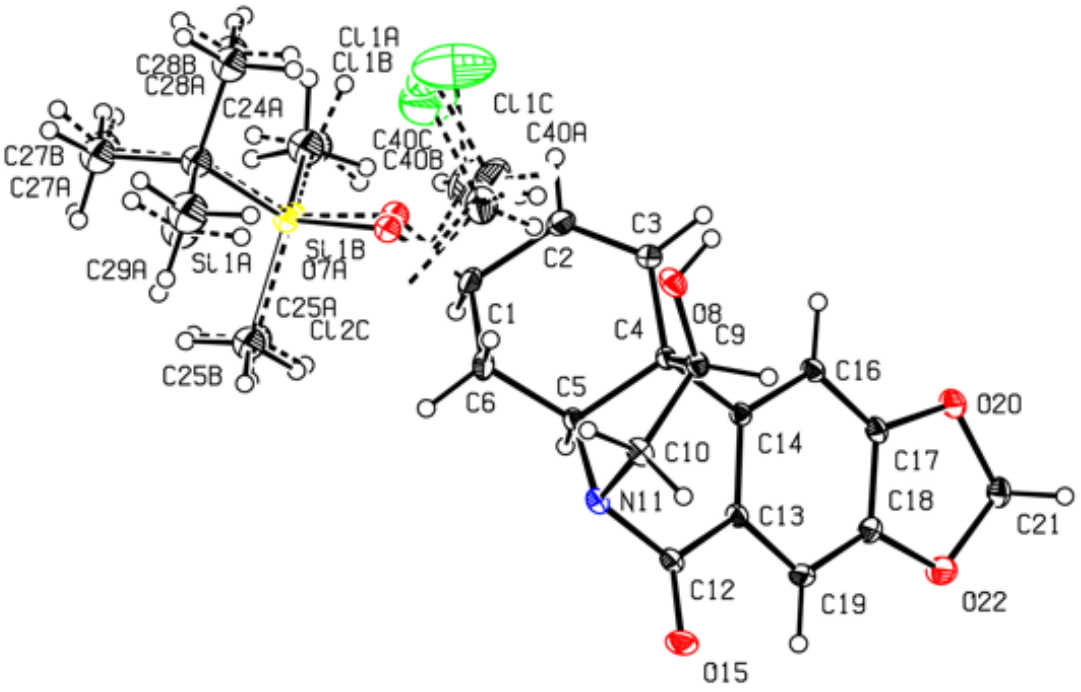


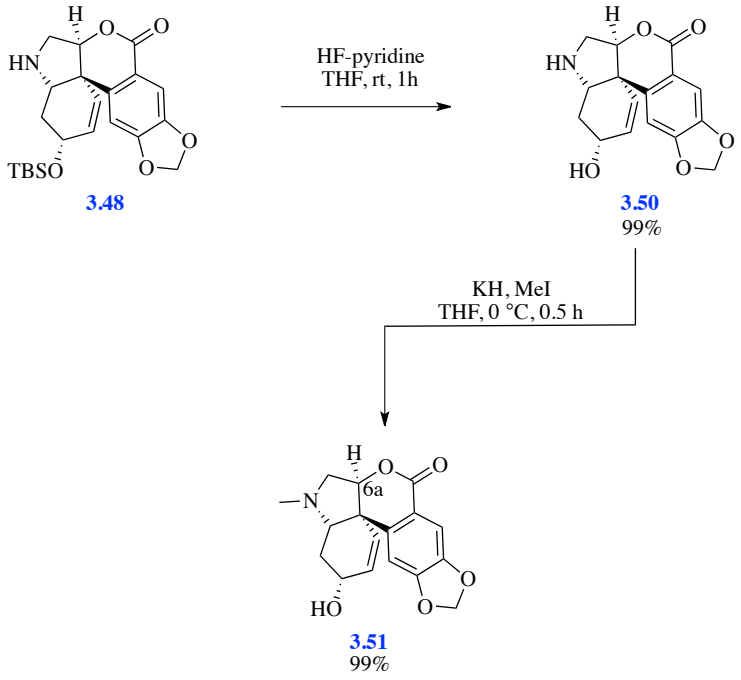
Figure 1.15: ORTEP Derived from the Single-Crystal X-ray Analysis of Compound 3.49.
(Proved by Xiang Ma)

Presumably compound **3.46** arises through initial reduction of the ketone carbonyl residue within precursor **3.22** such that the hydroxyl group within the resulting alcohol sits, as is evident from inspection of molecular models, directly above the lactam carbonyl moiety and can thus approach the latter along a Bürgi−Dunitz trajectory[61] and so facilitating its conversion into the isomeric lactone that is itself reduced to the observed mixture of lactols **3.46**. In contrast, the epimeric alcohol arising from reduction of the ketone residue within compound **3.22** is unable to readily engage in a lactam-to-lactone isomerisation process and so the residual (and strained) lactam carbonyl group is reduced directly to give compound **3.47**.

3.5.3 Completing Total Syntheses of the (±)-3-*O*-Demethylmacronine (1.68) and Its C6a-epimer

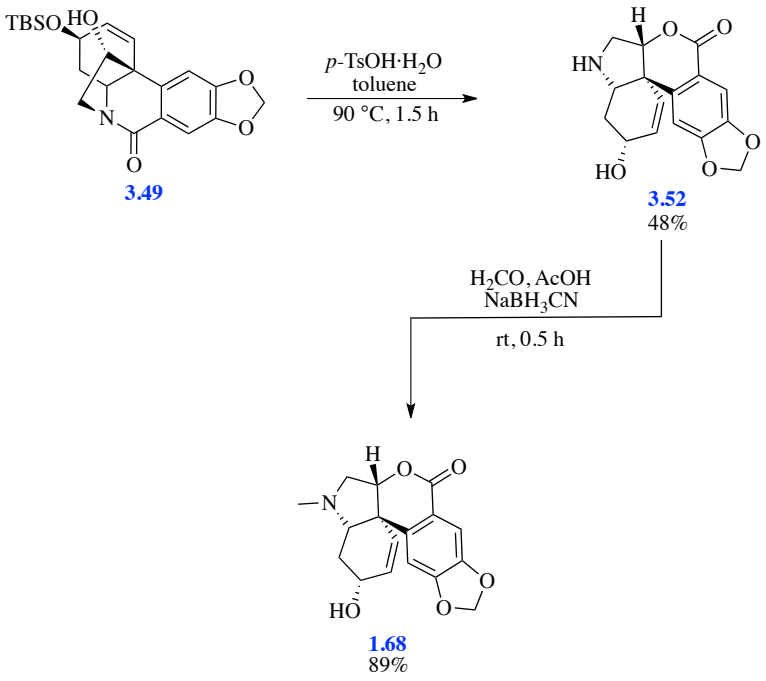
Because of time constraints, the work detailed from this point was undertaken by the author's colleague Mr Xiang Ma but is presented here for the sake of completeness. In

order to define a possible pathway for achieving a total synthesis of (±)-3-*O*-demethylmacronine (**1.68**) and so as to conserve material, the completion of the assembly of its C6a-epimer was first investigated. The ultimately straightforward synthetic pathway used to convert lactone **3.48** into compound **3.51**, the C6a-epimer of 3-*O*-demethyl-macronine, is shown in **Scheme 1.26**. Thus, treatment of silyl ether **3.48** with HF•pyridine in tetrahydrofuran at ambient temperatures for 1 h gave the expected allylic alcohol **3.50** in 99% yield and when this was treated with potassium hydride and methyl iodide in tetrahydrofuran at 0 °C for 0.5 h, the anticipated 3°-amine **3.51** was obtained in near quantitative yield. Interestingly, in the second step of this reaction sequence, no product arising from *O*-methylation of the allyic alcohol moiety was observed. The ^{1}H and ^{13}C NMR spectral data acquired on compound **3.51** were in complete accord with the assigned structure and quite distinct from those recorded for the natural product 3-*O*-demethylmacronine **1.68**.



Scheme 1.26: Conversion of Lactone 3.48 into the C6a-Epimer, 3.51, of (±)-3-O-Demethylmacronine.

The equivalent route used in completing the total synthesis of target **1.68** is shown in **Scheme 1.27**. This involved, as a pivotal step, the *p*-toluenesulfonic acid acid-promoted conversion of the haemanthidine-based hydroxylactam **3.49** into the lactone **3.52** (48%). Accompanying this process was the cleavage of the silyl ether associated with the starting material. The precise pathway by which this rearrangement takes place remains unclear. However, given the likely abnormally basic nature of the nitrogen associated with the bridged lactam[62] in substrate **3.49**, protonation at this centre, followed by cleavage of the N–C=O single bond then reaction of the resulting acylium ion with the pendant hydroxyl group, would afford the observed lactone **3.52**. Reductive *N*-methylation of compound **3.52** using sodium cyanoborohydride and formaldehyde in acetic acid at ambient temperatures then gave (±)-3-*O*-demethylmacronine (**1.68**) in 89% yield. Interestingly, attempts to effect the *O*-methylation of the last compound under a range of conditions[63] failed to generate (±)-macronine (**3.33**). While the origins of this situation are not clear, the likely close spatial arrangement of the hydroxyl and amine groups within compound (±)-**1.68** could be responsible.



Scheme 1.27: Completion of the Total Synthesis of (±)-3-O-Demethylmacronine (1.68).

All the spectral data acquired on compound **1.68** were in complete accord with the assigned structure, while the ^{1}H and ^{13}C NMR spectra recorded on the synthetic material matched those reported by Hesse[55] for the natural product (**Table 1**).

Table 1: Tabular Comparison of the ^{13}C NMR Chemical Shifts Recorded for Compound 1.68 with Those Reported for the Natural Product 3-O-Demethylmacronine

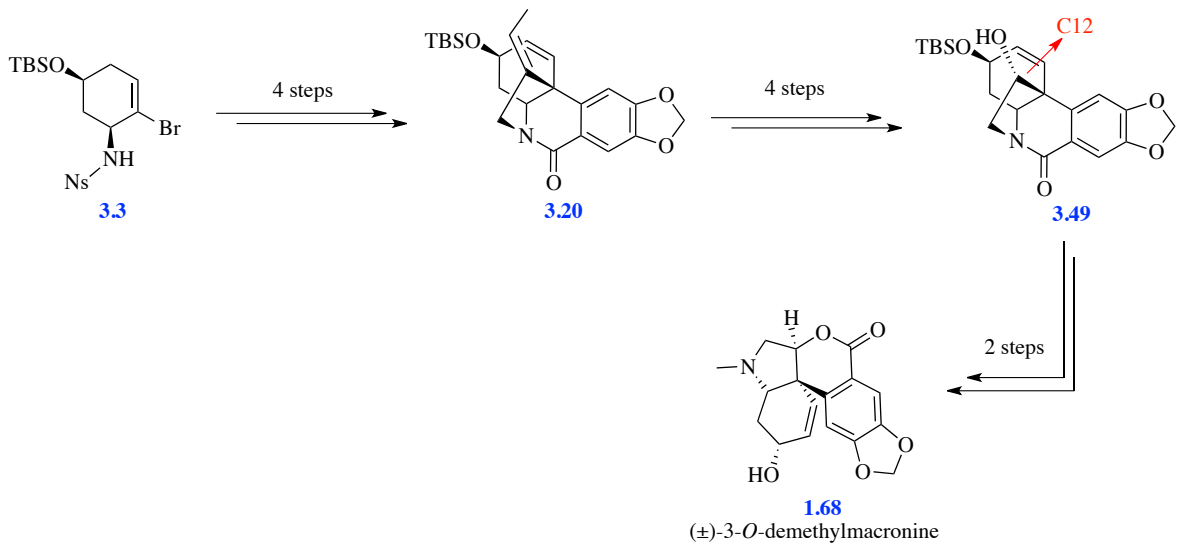
^{13}C NMR Data for Compound **1.68** (δ_C)[a]	^{13}C NMR Data for 3-*O*-Demethylmacronine (δ_C)[b]	$\Delta\delta$
167.2	167.3	–0.1
154.3	154.4	–0.1
148.9	149.0	–0.1
143.1	143.1	0
133.1	133.2	–0.1
127.2	127.3	–0.1
119.4	119.5	–0.1
111.3	111.5	–0.2
104.9	105.0	–0.1
103.9	104.0	–0.1
82.0	82.2	–0.2
65.6	65.7	–0.1
64.4	64.6	–0.2
53.7	53.8	–0.1
47.5	47.7	–0.2
42.9	43.0	–0.1
31.1	31.3	–0.2

[a] recorded in CD_3OD at 100 MHz;

[b] data obtained from Hesse,[55] spectrum recorded in CD_3OD at 150 MHz

3.6 Conclusion

This Chapter has detailed attempts by the author to establish a new route to the complex alkaloid gracilamine (**1.1**) that acknowledges the presence of the hydroxyl group on the E-ring. In the course of this work the formation of lactam **3.20** and lactone **3.27** were observed and given the relevance of the structure of the latter to the alkaloid 3-*O*-demethyl-macronine (**1.68**) the development of a synthesis of this novel natural product was pursued. So, the previously reported cycloalkenyl bromide **3.3** (**Scheme 1.28**) was converted over four steps into the strained lactam **3.20**. This was itself transformed into congener **3.49**, embedded within which is a C12-hydroxylated haemanthidine framework that could be engaged in a rearrangement reaction to generate the tetracyclic skeleton of the alkaloid (±)-3-*O*-demethylmacronine (**1.68**). Evidence has been presented to show that this rearrangement proceeds regardless of the stereochemistry at C-12 although the reaction pathways involved are quite different in each instance. While the biosynthetic relevance (or otherwise) of such reactions remain to be determined, this process should enable the preparation of various compounds possessing a range of molecular frameworks of biological interest.



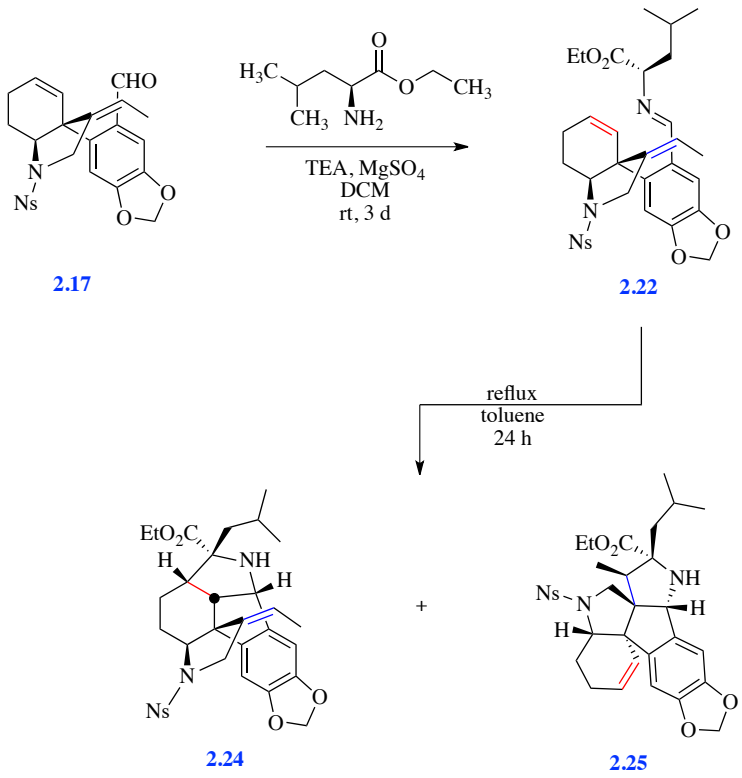
Scheme 1.28: Overview of the Total Synthesis of (±)-3-O-Demethylmacronine (1.68) Realised by the Author and Her Co-worker.

In summary, then, a ten-step synthesis of (±)-3-*O*-demethylmacronine (**1.68**) from readily available materials is reported, as is a synthesis of its C6a-epimer using related chemistry.

Chapter Four: Completion of a Total Synthesis of (±)-Gracilamine (1.1)

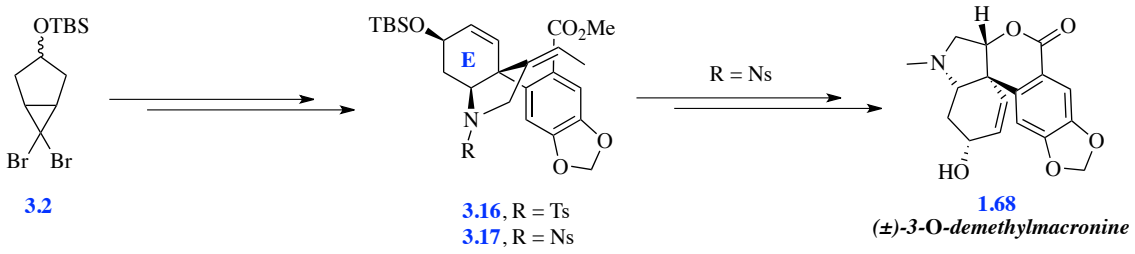
4.1 Overview of the Work Described in the Preceding Chapters

Chapter 2 detailed a model study that resulted in a successful, biomimetic means for assembling the polycyclic framework of gracilamine (**1.1**). The pivotal steps were, as shown in **Scheme 1.29**, a Schiff base condensation reaction between aldehyde **2.17** and ethyl *L*-leucinate followed by engagement of the ensuing imine **2.22** in an intramolecular [3+2]cycloaddition reaction and thereby forming, in essentially equal amounts, the chromatographically separable cycloadducts **2.24** and **2.25**. The first and desired adduct arises from addition of the ylide to the cyclohexanyl double bond within compound **2.17**, while the second derives from analogous addition to the exocyclic olefinic residue within this same substrate.



Scheme 1.29: Summary of the Key Steps Associated with Work Described in Chapter Two.

Chapter 3 describes the author's efforts to apply these results to the synthesis of gracilamine itself by acknowledging the presence of the E-ring hydroxyl group in the natural product. As part of these investigations efforts were made to the remove the exocyclic olefin associated with compounds **3.16** and **3.17**. While this proved difficult, because of the intervention of unanticipated lactamization reactions, the opportunity arose to effect a total synthesis of the natural product (±)-3-*O*-demethylmacronine (**1.68**) by the pathway shown in **Scheme 1.30**.

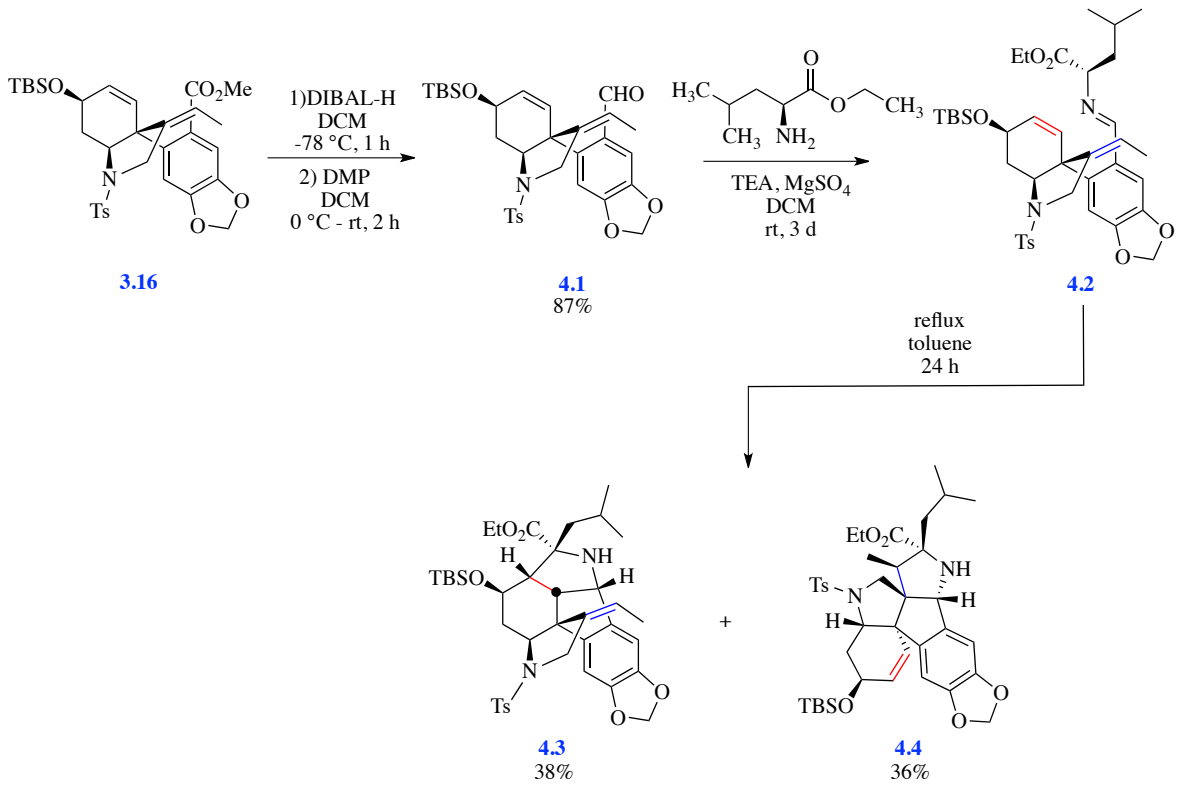


Scheme 1.30: A Summary of the Work Described in Chapter 3.

This Chapter details the author's identification of protocols for the successful deletion of the exocyclic double bond within compound **3.16** and, thereby, the completion of a total synthesis of (±)-gracilamine. As revealed below, the key to success was delaying the deletion of the exocyclic olefin associated with the IMAE product **3.16** until after the relevant [3+2]cycloaddition reaction had been carried out. Unsurprisingly, the "penalty" associated with adopting this approach was that a competing [3+2]cycloaddition reaction involving the exocyclic olefin had to be tolerated.

4.2 Assembling the Pentacyclic Framework of (±)-Gracilamine (1.1)

The previously reported sulfonamide **3.16** was carried forward to gracilamine (**1.1**) by the reaction pathway shown in **Scheme 1.31**. So, as previously described, the ester residue within compound **3.16** was converted, over two steps, into aldehyde **4.1** (87%) that was itself subjected to reaction with ethyl *L*-leucinate and so affording the expected Schiff base. Without exhaustive characterization, this base was subjected to thermolysis in refluxing toluene and, as a result, the anticipated and chromatographically separable mixture of the [3+2] cycloadducts **4.3** (38%) and **4.4** (36%) was obtained. All the spectroscopic and analytical data obtained on these cycloadducts were consistent with the assigned structures. In particular, a one-proton olefinic signal, appearing at δ 5.05 (m, 1H), was observed in the ^{1}H NMR spectrum of compound **4.3** (**Figure 1.16**), while in the analogous spectrum of congener **4.4** two mutually coupled olefinic proton resonances were observed at δ 5.77 (d, J = 10.2 Hz, 1H) and 5.20 (d, J = 10.2 Hz, 1H).



Scheme 1.31: Synthesis of Aldehyde 4.1 and Its Engagement in a Schiff-Base Condensation/[3+2]Cycloaddition Reaction Sequence Leading to Compounds 4.3 and Isomer 4.4.

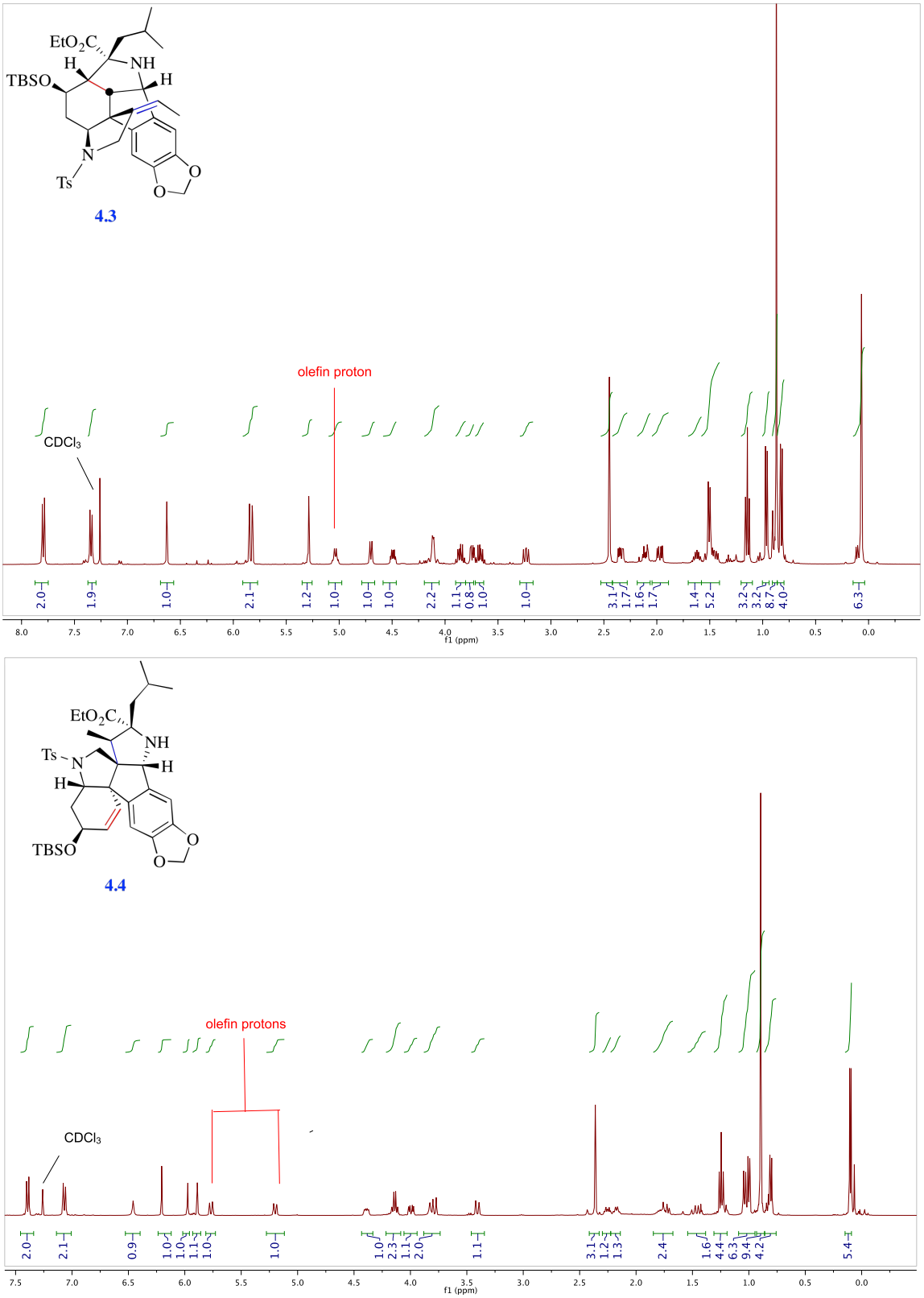
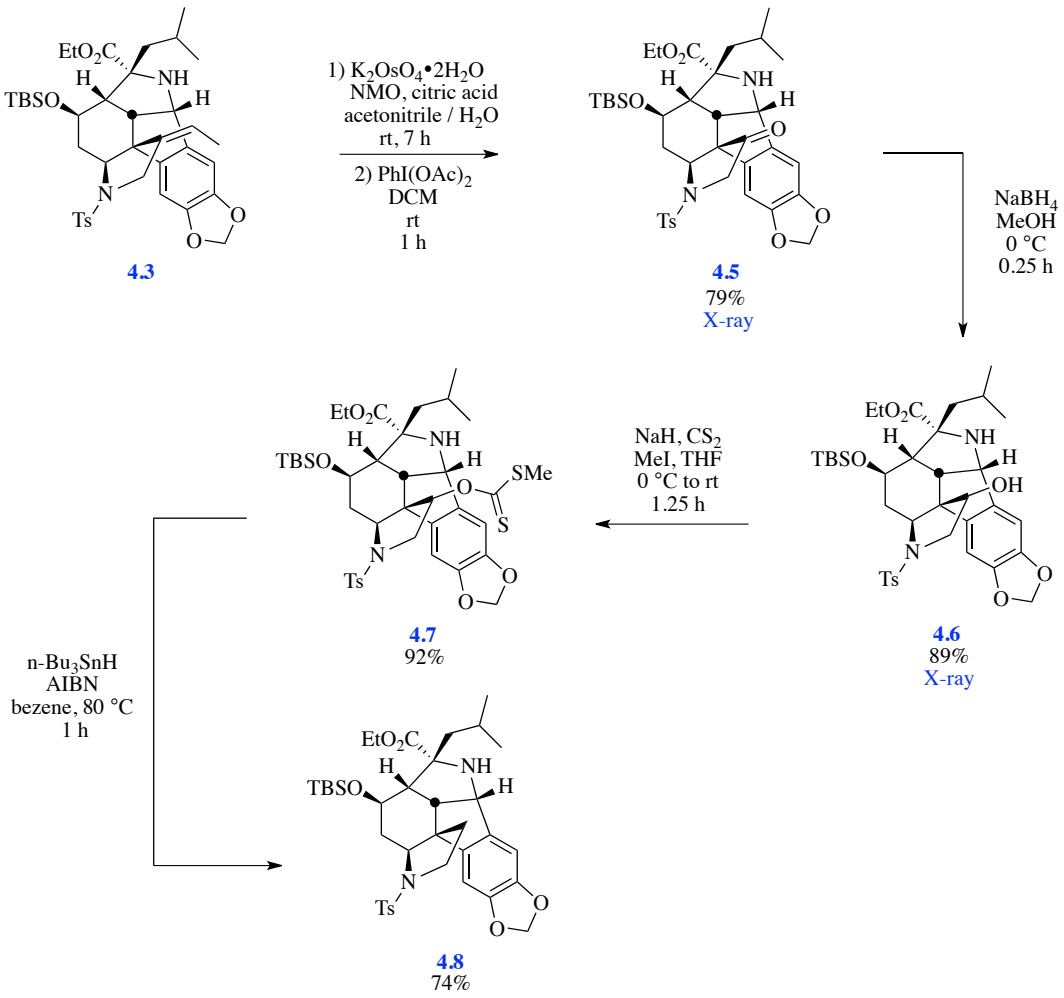


Figure 1.16: The 400 MHz ^{1}H NMR Spectra of Compounds 4.3 and 4.4 (recorded in $CDCl_3$) Highlighting the Olefinic Resonances Allowing for the Ready Assignment of Their Structures.

4.3 Deletion of the Exocyclic Olefinic Residue Associated with Cycloadduct 4.3

Compound **4.3** embodies the full pentacyclic ring system of gracilamine (**1.1**) and the associated exocyclic olefin was readily and efficiently converted into the corresponding ketone **4.5** (79%) through dihydroxylation of the first compound followed by iodobenzene diacetate-mediated oxidative cleavage of the product diol.[32a)] In order to completely remove the ketone moiety, a three-step and Barton-McCombie-based deoxygenation protocol was then used.[64] Thus, ketone **4.5** was first reduced, in a stereoselective manner, to the corresponding alcohol **4.6** (89%) using sodium borohydride in methanol. The structures of compounds **4.5** and **4.6** followed from the derived NMR, MS, and IR spectral data but were confirmed by single-crystal X-ray analyses on each of them. The resulting ORTEPs are shown in **Figures 1.17** and **1.18**, respectively, while further details of these analyses are presented in the Experimental Section.

Treatment of alcohol **4.6** with sodium hydride, carbon disulfide, and methyl iodide in tetrahydrofuran led to the formation of the methyl xanthate **4.7** (92%) (**Scheme 1.32**) and subjection of a refluxing benzene solution of this to reaction with tri-*n*-butyltin hydride and azobisisobutyronitrile then afforded the desired perhydroindole **4.8** in 74% yield.



Scheme 1.32: Deletion of the Exocyclic Double Bond Accomplished.

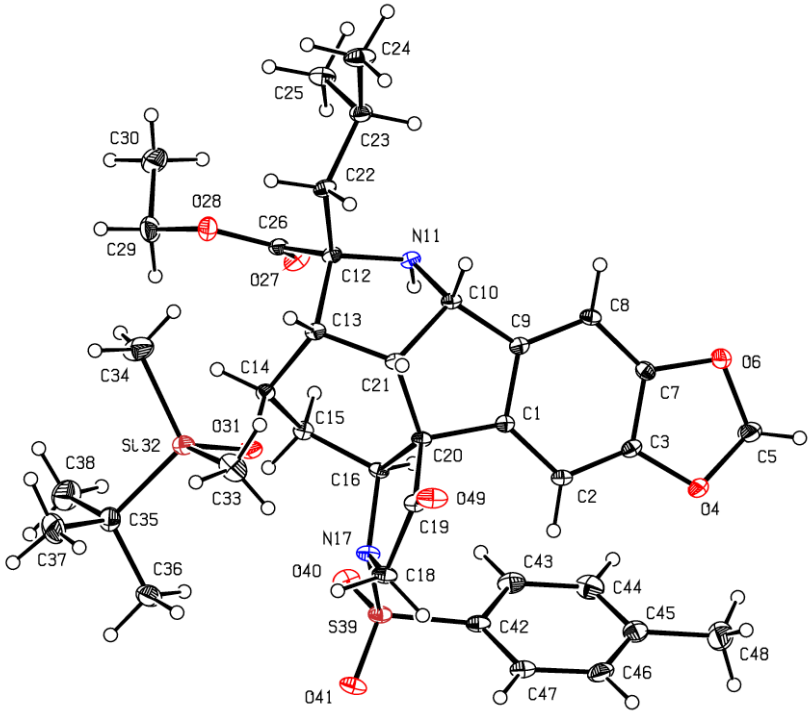


Figure 1.17: ORTEP Derived from the Single-Crystal X-ray Analysis of Compound 4.5.

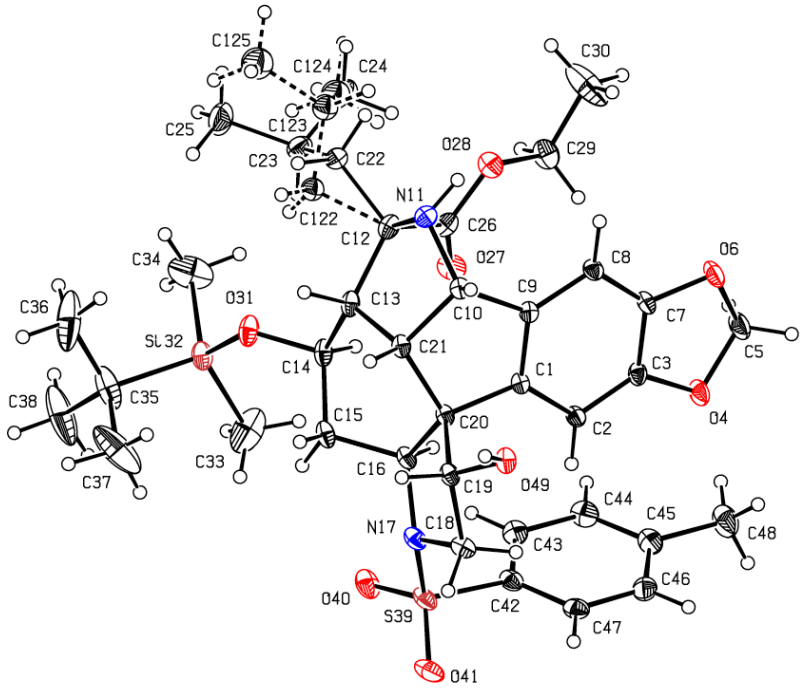
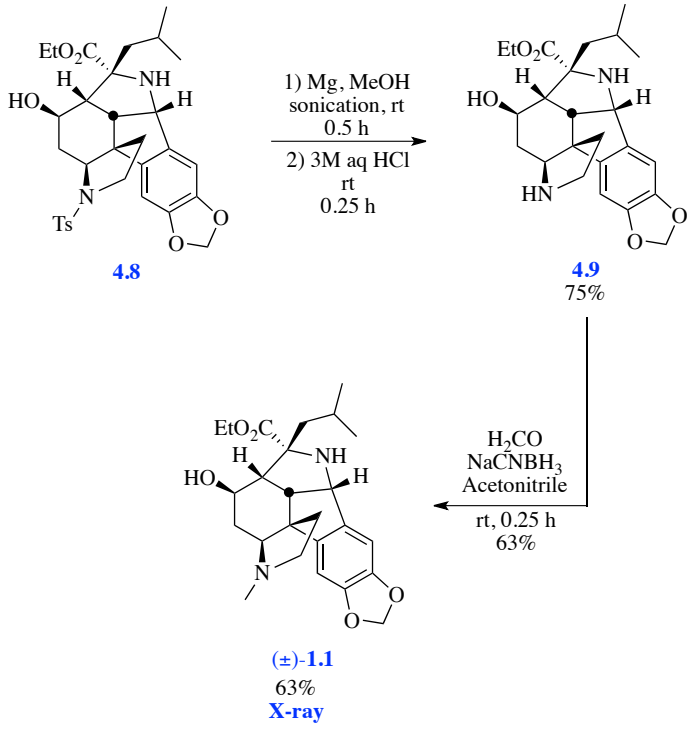


Figure 1.18: ORTEP Derived from the Single-Crystal X-ray Analysis of Compound 4.6.

4.4 Completion of a Total Synthesis of (±)-Gracilamine (1.1)

The completion of the author's by now long-sought-after total synthesis of (±)-gracilamine (**1.1**) is shown in **Scheme 1.33**. Thus, treatment of the compound **4.8** with magnesium in methanol under sonication led to cleavage of the sulfonamide residue and subjection of the resulting amine to reaction with 3 M aqueous hydrochloric acid effected cleavage of the TBS-ether and thus generating norgracilamine **4.9** in 75% yield. Eschweiler-Clarke-type methylation of compound **4.9** using formaldehyde and sodium cyanoborohydride then gave (±)-gracilamine (**1.1**) itself in 63% yield. The assignment of structure (±)-**1.1** to this end product followed from the usual acquisition of NMR, MS, and IR spectral data but was subsequently confirmed by single-crystal X-ray analysis (see **Figure 1.19** and the Experimental Section for details). Furthermore, all of the ^{1}H and ^{13}C NMR spectral data obtained on the synthetically derived sample of (±)-gracilamine were in complete agreement (see **Table 2**) with those reported by both Ma[2] and Gao[9] for their materials, and with those reported by Ünver and Kaya[1] for the naturally-derived compound.



Scheme 1.33: Completion of a Total Synthesis of (±)-Gracilamine (1.1).

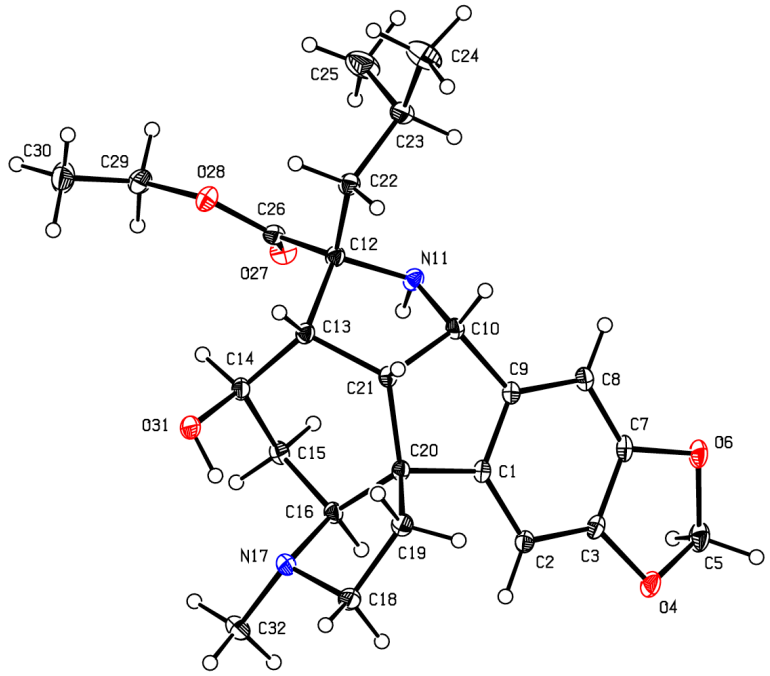


Figure 1.19: ORTEP Derived from the Single-Crystal X-ray Analysis of Compound (±)-1.1.

Table 2: ***Comparison of the ^{13}C NMR Spectral Data Reported by Ma[2] and Gao[9] for Gracilamine with the Equivalent Data Recorded for Compound (±)-1.1 Prepared by the Present Route***

δ_C (*ex*. Ma)[a]	δ_C (*ex*. Gao)[b]	δ_C (*ex*. Present Route)[c]	$\Delta\delta$ δ_C(PR[d]) –δ_C(Gao)
175.8	175.9	175.8	–0.1
150.2	150.1	150.1	0
149.3	149.1	149.1	0
143.8 (broadened)	144.7	144.4	–0.3
136.5	136.3	136.4	+0.1
106.0	105.7	105.8	+0.1
103.6	103.8	103.7	–0.1
102.8	102.7	102.7	0
74.1	74.3	74.2	–0.1

71.3	71.2	71.2	0
67.7	67.7	67.7	0
66.4	66.5	66.5	0
62.2	62.1	62.1	0
58.5	58.8	58.8	0
55.7	56.9	56.5 (broadened)	–0.4
55.6	55.6	55.6	0
54.6	54.7	54.7	0
48.1	47.4	47.7	+0.3
45.0	45.5	45.3	–0.2
40.8	40.8	40.8	0
34.4 (broadened)	35.9	35.5 (broadened)	–0.4
26.4	26.3	26.3	0
24.8	24.9	24.9	0
23.7	23.5	23.6	+0.1
14.2	14.1	14.1	0

([a] Spectrum recorded in CD_3OD at 100 MHz; [b] Spectrum recorded in CD_3OD at 100 MHz; [c] Spectrum recorded in CD_3OD at 175 MHz; [d] PR = present route.)

4.5 Conclusion

As summarised in **Scheme 1.31**, the present work has provided a new route to (±)-gracilamine (**1.1**) starting from the previously reported and ring-fused *gem*-dibromocyclopropane **3.2**. Key transformations leading from this "starting material" to compound **4.1** included thermally-induced electrocyclic ring-opening and Pd[0]-catalyzed intramolecular alder-ene reaction (IMAE) reactions. The illustrated azomethine ylide **4.2**, obtained through a Schiff-base condensation of the corresponding aldehyde **4.1** embodying C3a-arylhexahydroindole, with ethyl *L*-lucinate, was engaged in a thermally-induced and stereoselective (but not regioselective) intramolecular [3+2]cycloaddition reaction mimicking the proposed biogenesis[v] of the pentacyclic framework of compound **1.1**. The

pentacyclic framework **4.3** so-formed was then elaborated, over a further eight steps, into the racemic modification of the alkaloid derivative gracilamine (**1.1**).

Compared with previous syntheses,[2, 9, 19, 13] this route only required eleven steps to assemble the complete polycyclic framework of the target alkaloid.

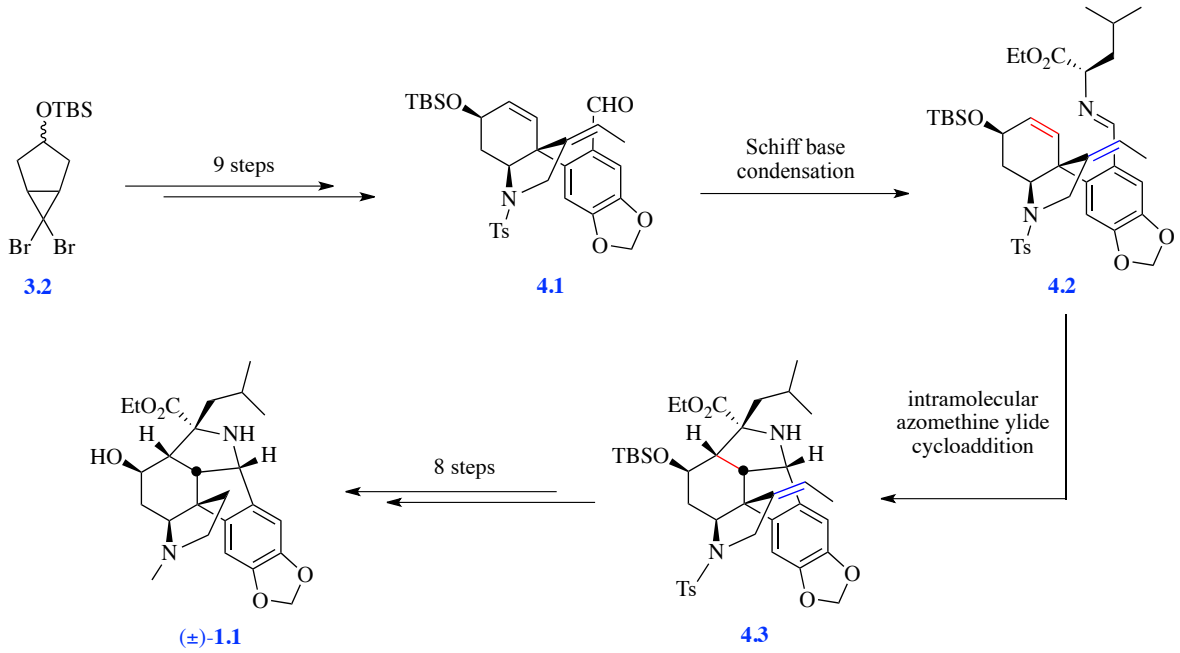


Figure 1.20: Summary the Author's Total Synthesis of (±)-Gracilamine (1.1).

Chapter Five: Experimental Procedures Associated with the Work Described in Chapter Two to Four

5.1. General Experimental Procedures

Starting materials and reagents were generally available from Sigma-Aldrich, Merck, TCI, AK Scientific, Stem and were used as supplied or, occasionally, recrystallised or distilled. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran, dichloromethane, *N*,*N*-dimethylformamide, diethyl ether, hexane and toluene were dried using a Glass Contour™ solvent purification system that is based upon a technology originally described by Grubbs *et al*.[65]

Glassware was soaked in a base bath (pyroneg in water) before being rinsed with distilled water then acetone before being oven-dried at 120 °C. Assembled apparatus was evacuated (<0.1 mm Hg) and flushed three times with dry nitrogen prior to use. All reaction mixtures were manipulated under nitrogen using standard schlenk techniques and, unless otherwise specified, stirred magnetically.

Ambient temperature was assumed to be *ca*. 22 °C. Temperatures higher than ambient were attained using thermostated oil baths. To attain temperatures lower than ambient, a cooled, water-circulating bath (0 to 10 °C) or relevant cryostats (ice/water, 0 °C; dry-ice/acetone, −78 °C) were used.

Organic solutions (extracts) obtained from the work-up of reaction mixtures were dried with sodium sulfate (Na_2SO_4) or magnesium sulfate ($MgSO_4$) before being filtered and concentrated under reduced pressure on a rotary evaporator with water bath temperature generally not exceeding 40 °C unless otherwise specified.

Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a

254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included: a) potassium permanganate: potassium carbonate: 5% sodium hydroxide aqueous solution: water (3g : 20g : 5 mL : 300mL); b) anisaldehyde : sulfuric acid (conc.) : ethanol (3 mL : 4.5 mL : 200 mL); c) vanillin : sulfuric acid (conc.) : ethanol : water (18g : 3 mL : 285 mL : 15 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al*.[66] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated.

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a Varian spectrometer operating at 400 MHz for proton and 101 MHz for carbon nuclei. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. Chemical shifts are recorded as δ values in parts per million (ppm). ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.16 were used to reference ^{1}H and proton-decoupled ^{13}C NMR spectra, respectively. For ^{13}C NMR spectra, the data are given as: chemical shift (δ).

Infrared spectra (ν_{max}) were sometimes recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer with the samples being presented as thin films on KBr plates. Samples analyzed by attenuated total reflectance (ATR) IR spectroscopy were prepared by allowing a $CDCl_3$ solution of these to evaporate on the sampling plate before the spectrum was acquired.

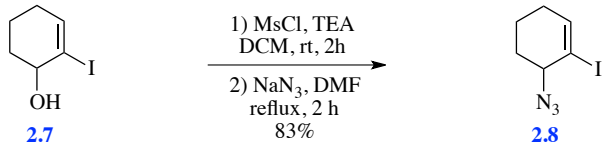
Mass spectrometry was performed by the Australian National University's Mass Spectrometric Services Unit located in the Research School of Chemistry, Canberra, Australia. Low-resolution ESI mass spectra were recorded on a single-quadrupole liquid chromatograph−mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution electron impact (EI) mass spectra were recorded on a magnetic-sector machine.

Chapter Five: Experimental Procedures Associated with the Work Described in Chapter Two to Four

Melting points were recorded on an Optimelt™ automated melting point system and are uncorrected.

5.2 Experimental Procedures Related to Work Described in Chapter Two

(±)-6-Azido-1-iodocyclohex-1-ene [(±)-2.8]



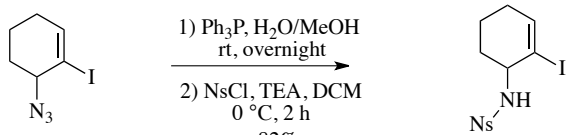
Step i: A magnetically stirred solution of 2-iodocyclohex-2-enol (**2.7**)[67] (1.00 g, 4.46 mmol) in dichloromethane (30.0 mL) maintained at 0 °C was treated with triethylamine (1.20 mL, 8.92 mmol) then methanesulfonyl chloride (620 mg, 5.41 mmol). The ensuing mixture was stirred at 22 °C for 2 h before being diluted with ethyl acetate (100 mL) then water (50.0 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 50.0 mL) and the combined organic phases then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing light-brown oil was subjected, without purification, to *step ii* of the reaction sequence as detailed immediately below.

Step ii: The light-brown oil obtained from *step i* was dissolved in *N*,*N*-dimethylformamide (30.0 mL) and the resulting solution treated, at 22 °C, with sodium azide (435 mg, 6.69 mmol) then allowed to stir at 80 °C for 2 h before being cooled then diluted with ethyl acetate (30.0 mL) and water (30.0 mL). The separated organic phase was washed with water (4 × 30.0 mL) and brine (1 × 30.0 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica gel, 4:1 *v/v* hexane/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.7 in 3:1 *v/v* hexane/ethyl acetate) gave azide **2.8** (922 mg, 83%) as clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.64 (t, J = 4.4 Hz, 1H), 3.98 (m, 1H), 2.22-2.06 (complex m, 2H), 2.06-1.94 (complex m, 2H), 1.78-1.69 (complex m, 2H);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 143.1, 94.6, 64.7, 30.7, 29.2, 17.4;
IR (KBr) ν_{max} 2925, 2852, 2097, 1626, 1441, 1244, 990, 803 cm^{-1};

MS (EI, 70 eV) *m/z* 249 ($M^{+\bullet}$, 83%), 207 (50), 206 (100), 205 (65), 79 (82);
HRMS (EI) Calculated for $C_6H_8IN_3$: 248.9763. Found: 248.9775.

(±)-*N*-(2-Iodocyclohex-2-en-1-yl)-2-nitrobenzenesulfonamide [(±)-2.9]



2.8 **2.9**

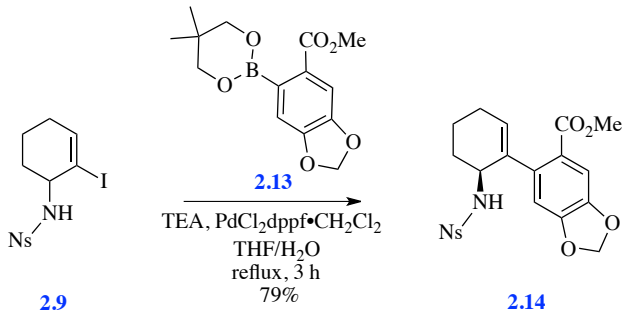
Step i: A magnetically stirred solution of compound **2.8** (2.00 g, 8.03 mmol) in methanol/water (100 mL of a 95:5 *v/v* mixture) was treated with triphenylphosphine (3.67 g, 14.5 mmol) and the ensuing mixture stirred at 22 °C overnight. After this time the reaction mixture was diluted with ethyl acetate (100 mL) then water (50.0 mL) and the separated aqueous phase extracted with ethyl acetate (2 × 50.0 mL). The combined organic phases were dried ($MgSO_4$), filtered then concentrated under reduced pressure. The yellow oil thus obtained was subjected to flash chromatography (silica gel, 4:1 *v/v* hexane/ethyl acetate) to give, after concentration of the relevant fractions (R_f = 0.3 in 4:1 *v/v* hexane/ethyl acetate), a clear, colourless oil. This material, assumed to contain the anticipated 1°-amine, was subjected, without purification, to *step ii* of the reaction sequence as detailed immediately below.

Step ii: The clear, colourless oil obtained from *step i* was dissolved in dry dichloromethane (30.0 mL) and the resulting solution cooled to 0 °C then treated with triethylamine (1.29 mL, 9.64 mmol) and nosyl chloride (1.84 g, 9.64 mmol). The ensuing mixture was stirred at 0 °C for 2 h then diluted with dichloromethane (20.0 mL) and water (20.0 mL). The separated aqueous phase was extracted with dichloromethane (2 × 20.0 mL) and the combined organic phases washed with brine (1 × 50.0 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash chromatography (silica gel, 4:1 *v/v* hexane/ethyl acetate) gave, after concentration of the appropriate fractions (R_f = 0.7 in 4:1 *v/v* hexane/ethyl acetate),

compound **2.9** (2.69 g, 82%) as white, crystalline solid, m.p. = 125-127 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.17 (m, 1H), 7.93 (m, 1H), 7.74 (m, 2H), 6.54 (t, J = 4.4 Hz, 1H), 5.61 (d, J = 6.8 Hz, 1H), 4.07 (broadened s, 1H), 2.21-2.01 (complex m, 3H), 1.96-1.88 (complex m, 1H), 1.76-1.69 (complex m, 2H);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 148.0, 144.5, 134.7, 133.7, 133.1, 130.9, 125.7, 94.6, 59.4, 32.7, 29.3, 16.2;
IR (KBr) ν_{max} 3348, 3096, 2937, 1537, 1442, 1406, 1356, 1167, 1059, 732 cm^{-1};
MS (ESI, +ve) *m/z* 431 [$(M+Na)^+$, 100%], 264 (95), 224 (80);
HRMS (ESI, +ve) $(M + Na)^+$, Calculated for $C_{12}H_{13}IN_2NaO_4S$: 430.9539. Found: 430.9535.

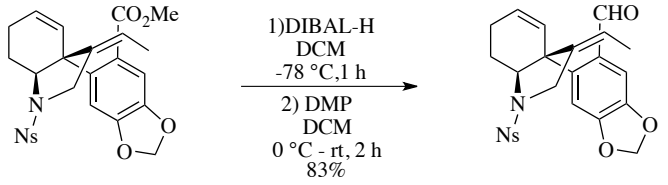
(±)- (*S*)-Methyl 6-(6-(2-Nitrophenylsulfonamido)cyclohex-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate [(±)-2.14]



A magnetically stirred solution of compound **2.9** (3.50 g, 8.58 mmol), methyl 6-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzo[*d*][1,3]dioxole-5-carboxylate (**2.13**)[36] (2.74 g, 17.2 mmol), $PdCl_2dppf•CH_2Cl_2$ (314 mg, 0.429 mmol) and triethylamine (1.39 mL, 10.3 mmol) in tetrahydrofuran/water (120 mL of a 9:1 *v/v* mixture) was purged with nitrogen for 0.25 h then heated under reflux for 3 h before being cooled, quenched with water (50.0 mL) and then extracted with ethyl acetate (3 × 50.0 mL). The combined organic layers were washed with brine (1 × 50.0 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing brown oil was subjected to flash chromatography (silica, 4:1 *v/v* hexane/ethyl acetate) to afford, after concentration of the appropriate fractions (R_f = 0.6 in

7:3 *v/v* hexane/ethyl acetate), compound **2.14** (3.12 g, 79%) as white, crystalline solid. The spectral and physical data derived from this material matched those reported previously.[28]

(±)-6-((3a*R*,7a*S*,*Z*)-3-Ethylidene-1-((2-nitrophenyl)sulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indol-3a-yl)benzo[*d*][1,3]dioxole-5-carbaldehyde [(±)-2.17]



2.16 **2.17**

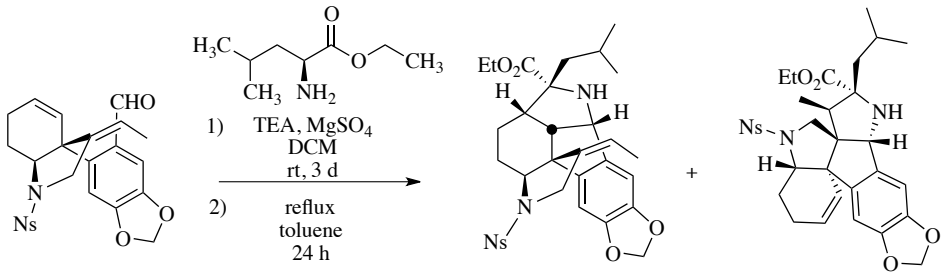
Step i: A magnetically stirred solution of compound **2.16**[28] (400 mg, 0.780 mmol, prepared over three previously defined[28] steps from sulfonamide **2.9**) in dichloromethane (25.0 mL) maintained under nitrogen was cooled to −78 °C then treated, dropwise, with DIBAl-H (3.12 mL of a 1 M solution in tetrahydrofuran, 3.12 mmol). The ensuing mixture was stirred at −78 °C for 5 h then quenched with tartaric acid (20.0 mL of a 1 M aqueous solution) and after stirring for 0.5 h the separated aqueous phase was extracted with dichloromethane (2 × 30.0 mL). The combined organic phases were then dried ($MgSO_4$) before being filtered then concentrated under reduced pressure. The clear, colourless oil thus obtained was subjected to flash chromatography (silica gel, 4:1 *v/v* hexane/ethyl acetate) to give, after concentration of the relevant fractions (R_f = 0.4 in 7:3 *v/v* hexane/ethyl acetate), a white, crystalline solid. This material, assumed to be the anticipated benzyl alcohol, was subjected, without purification, to *step ii* of the reaction sequence as detailed immediately below.

Step ii: The crystalline solid obtained from *step i* was dissolved in dry dichloromethane (20.0 mL) and the resulting solution cooled to 0 °C then treated with the Dess-Martin periodinane (345 mg, 0.940 mmol). The ensuing mixture was stirred at 0 °C for 1 h then treated with brine (10.0 mL). The separated aqueous phase was extracted with dichloromethane (2 × 20.0 mL) and the combined organic phases dried (Na_2SO_4), filtered and concentrated under reduced pressure. The light-brown oil thus obtained was subjected to flash chromatography (silica gel, 4:1 *v/v* hexane/ethyl acetate) to afford, after

concentration of the appropriate fractions (R_f = 0.6 in 7:3 *v/v* hexane/ethyl acetate), compound **2.17** (312 mg, 83%) as a white, crystalline solid, m.p. = 175-176 °C.

^{1}H NMR (700 MHz, $CDCl_3$) δ_H δ 9.96 (s, 1H), 7.79 (m, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.48 (m, 1H), 7.22 (s, 1H), 6.85 (s, 1H), 5.98 (ABq, *J* = 17.6 Hz, 2H), 5.92 (m, 1H), 5.60 (m, 1H), 5.23 (m, 1H), 4.46 (d, *J* = 14.9 Hz, 1H), 4.35-4.27 (complex m, 2H), 2.35-2.28 (complex m, 1H), 2.20-2.11 (complex m, 1H), 2.05 (m, 1H), 1.83 (m, 1H), 1.68 (d, *J* = 6.7 Hz, 3H);
^{13}C NMR (175 MHz, $CDCl_3$) δ_C 188.8, 151.5, 148.1, 147.1, 143.1, 142.4, 133.4, 131.5, 131.3, 130.5, 128.8, 127.4, 124.0, 110.8, 109.8, 102.2, 67.3, 55.2, 49.8, 22.9, 14.8, 14.3 (two signals obscured or overlapping);
IR (KBr) ν_{max} 2919, 2814, 1673, 1610, 1544, 1505, 1482, 1372, 1355, 1256, 1166, 1127, 1069, 1037, 910, 729 cm^{-1};
MS (ESI, +ve) *m/z* 505 [$(M+Na)^+$, 100%];
HRMS (ESI, +ve) $(M + Na)^+$, Calculated for $C_{24}H_{22}N_2NaO_7S$: 505.1045. Found: 505.1046.

(±)-Ethyl (3a*S*,5a*S*,6*R*,7a*S*,12b*R*,*Z*)-1-Ethylidene-6-isobutyl-3-((2-nitrophenyl)sulfonyl)-2,3,3a,4,5,5a,5a^1,6,7,7a-decahydro-1*H*-[1,3]dioxolo[4',5':5,6]indeno[1,2,3-*cd*]pyrrole [3,2-*e*]isoindole-6-carboxylate (2.24) and Ethyl (4a*S*,6a*S*,7*R*,8*R*,9a*R*,14b*R*)-8-Iso-butyl-7-methyl-5-((2-nitrophenyl)sulfonyl)-4,4a,5,6,7,8,9,9a-octahydro-3*H*-[1,3]dioxolo[4',5':5,6]pyrrolo[3',2':2,3]indeno[2,1-*c*]indole-8-carboxylate [(±)-2.25]



2.17 | **2.24** 36% | **2.25** 32%

A magnetically stirred solution of compound **2.17** (250 mg, 0.520 mmol) in dichloromethane (20.0 mL) maintained under a nitrogen atmosphere at 22 °C was treated, successively, with *L*-Leu-OEt•HCl (300 mg, 1.53 mmol), triethylamine (221 μL, 1.53 mmol) and anhydrous $MgSO_4$ (300 mg, 7.82 mmol). The resulting mixture was stirred at 22 °C for 72 h then concentrated under reduced pressure. The residue thus obtained was treated with toluene (20 mL) and the ensuing solution heated under reflux for 24 h then cooled and concentrated under reduced pressure. The brown oil thus obtained was subjected to flash chromatography (silica gel, 9:1 *v/v* hexane/ethyl acetate) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.7 in 3:1 *v/v* hexane/ethyl acetate) compound **2.24** (116 mg, 36%) as white solid, m.p. = 191-193 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.03 (dd, *J* = 7.7 and 1.6 Hz, 1H), 7.75-7.59 (complex m, 3H), 6.74 (s, 1H), 5.96 (s, 1H), 5.84 (s, 2H), 5.05 (m, 1H), 4.60 (d, *J* = 8.8 Hz, 1H), 4.51 (d, *J* = 15.5 Hz, 1H), 4.20 (d, *J* = 15.5 Hz, 1H), 4.15 (m, 2H), 3.84 (dd, *J* = 10.5 and 5.9 Hz, 1H), 3.21 (t, *J* = 8.9 Hz, 1H), 2.24-2.11 (complex m, 2H), 2.08 (m, 1H), 1.87-1.77 (complex m, 2H), 1.69 (m, 1H), 1.58 (d, *J* = 6.9 Hz, 3H), 1.47 (m, 1H), 1.32 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 6.2 Hz, 3H), 0.82 (d, *J* = 6.2 Hz, 3H), 0.78 (m, 1H) (signal due to N-H group proton not observed);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.0, 148.8, 148.2, 147.7, 145.7, 143.4, 134.3, 133.9, 133.0, 131.8, 130.8, 124.2, 118.5, 104.4, 103.0, 101.4, 76.4, 67.5, 67.2, 61.1, 58.5, 54.4, 49.5, 48.9, 44.1, 28.6, 25.1, 24.6, 22.5, 22.0, 14.8, 14.3;
IR (KBr) ν_{max} 3400, 2924, 2028, 1727, 1546, 1477, 1371, 1262, 1164, 1039 cm^{-1};
MS (ESI, +ve) *m/z* 624 [$(M+H)^+$, 100%];
HRMS (ESI, +ve) $(M + H)^+$, Calculated for $C_{32}H_{38}N_3O_8S$: 624.2380. Found: 624.2383.

Concentration of fraction B (R_f = 0.8 in 3:1 *v/v* hexane/ethyl acetate) gave compound **2.25** (103 mg, 32%) as white, crystalline solid, m.p. = 189-191 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.56 (m, 2H), 7.46-7.36 (complex m, 2H), 6.47 (s, 1H), 6.33 (s, 1H), 5.96 (m, 1H), δ 5.92 (d, *J* = 1.3 Hz, 1H), 5.86 (d, *J* = 1.3 Hz, 1H), 5.30 (d, *J* = 10.1 Hz, 1H), 4.12 (q, *J* = 10.1 Hz, 2H), 4.08 (s, 1H), 3.95 (dd, *J* = 10.5 and 4.2 Hz, 1H), 3.81 (m, 2H), 2.18 (m, 2H), 1.97 (m, 2H), 1.82 (m, 1H), 1.73 (m, 2H), 1.30 (dd, *J* = 13.8 and 4.4 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 6H), 0.80 (d, *J* = 6.5 Hz, 3H) (signal due to N-H group proton not observed);

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.4, 159.9, 148.5, 147.9, 140.2, 135.4, 133.0, 132.9, 131.2, 130.0, 129.2, 128.9, 123.7, 104.9, 104.6, 101.4, 74.9, 73.0, 67.6, 65.7, 62.4, 61.3, 53.2, 48.1, 39.6, 26.3, 24.8, 22.6, 22.5, 14.2, 11.3 (one resonance obscured or overlapping);

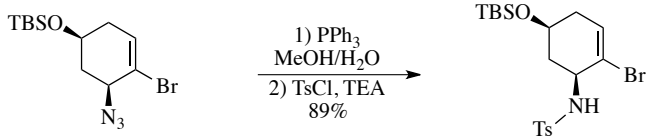
IR (KBr) ν_{max} 3405, 2958, 2028, 1723, 1545, 1477, 1372, 1252, 1165, 1128, 1038, 939, 852, 800 cm^{-1};

MS (ESI, +ve) *m/z* 624 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) $(M + H)^+$, Calculated for $C_{32}H_{38}N_3O_8S$: 624.2380. Found: 624.2377.

5.3 Experimental Procedures Related to Work Described in Chapter Three

(±)-*N*-((1*S*,5*S*)-2-Bromo-5-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)-4-methylbenzenesulfonamide [(±)-3.10]



3.3 **3.10**

Step i: A magnetically stirred solution of **3.3**[32a] (2.00 g, 6.04 mmol) in methanol/water (100 mL of a 95:5 *v/v* mixture) was treated with triphenylphosphine (3.06 g, 12.1 mmol) and the ensuing mixture stirred at 22 °C overnight then diluted with ethyl acetate (100 mL) and water (50.0 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 50.0 mL) and the combined organic phases dried ($MgSO_4$), filtered and concentrated under reduced pressure. The brown oil thus obtained was subjected to flash chromatography

(silica gel, 4:1 *v/v* hexane/ethyl acetate) to give, after concentration of the relevant fractions (R_f = 0.4 in 7:3 *v/v* hexane/ethyl acetate), a clear, colourless oil. This material, assumed to contain the anticipated 1° amine, was subjected, without purification, to *step ii* of the reaction sequence as detailed immediately below.

Step ii: The oil obtained from *step i* was dissolved in dry dichloromethane (20.0 mL) and the resulting solution cooled to 0 °C then treated with triethylamine (2.43 mL, 18.1 mmol) and tosyl chloride (1.40 g, 7.34 mmol). The ensuing mixture was stirred at 0 °C for 2 h then diluted with dichloromethane (20.0 mL) and water (20.0 mL). The separated aqueous phase was extracted with dichloromethane (2 × 20.0 mL) and the combined organic phases then washed with brine (1 × 50.0 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash chromatography (silica, 7:1 *v/v* hexane/ethyl acetate) gave, after concentration of the appropriate fractions (R_f = 0.5 in 4:1 *v/v* hexane/ethyl acetate), compound **3.10** (2.59 g, 89%) as white, crystalline solid, m.p. = 153-155 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.80 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 6.03 (t, J = 4.2 Hz, 1H), 5.77 (d, J = 9.7 Hz, 1H), 4.20 (m, 1H), 4.03 (broadened t, J = 7.8 Hz, 1H), 2.42 (s, 3H), 2.21 (m, 2H), 2.05 (m, 1H), 1.90 (m, 1H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H);

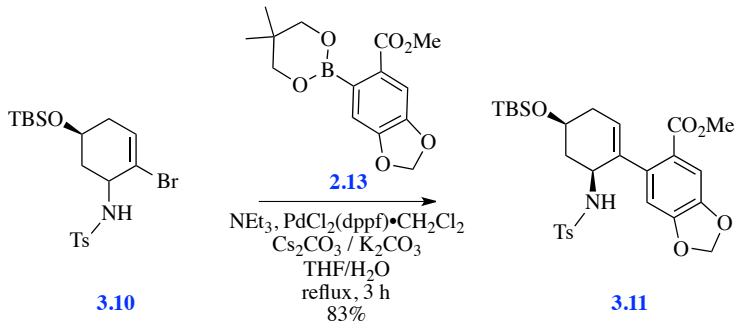
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 143.3, 138.5, 129.5, 128.7, 127.6, 121.9, 64.8, 54.0, 37.0, 36.0, 26.1, 21.7, 18.2, –4.8, –4.9 (four signal obscured or overlapping);

IR (KBr) ν_{max} 3332, 2954, 2929, 2857, 1649, 1598, 1471, 1410, 1338, 1281, 1258, 1160, 1093, 1058, 1019, 952, 905, 853, 837 cm^{-1};

MS (ESI, +ve) *m/z* 484 and 482 [$(M+Na)^+$, 100 and 85%];

HRMS (ESI, +ve) $(M + Na)^+$, Calculated for $C_{19}H_{30}{}^{81}BrNNaO_3SSi$: 484.0776. Found: 484.0772.

(±)-Methyl 6-((4*S*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-(4-methylphenylsulfonamido)cyclohex-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate [(±)-3.11]



A magnetically stirred solution of compound **3.10** (2.05 g, 4.47 mmol), methyl 6-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzo[*d*][1,3]dioxole-5-carboxylate (**2.13**)[36] (2.74 g, 8.94 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (256 mg, 0.310 mmol), potassium acetate (438 mg, 4.47 mmol) and cesium carbonate (1.46 mg, 4.47 mmol) in tetrahydrofuran/water (100 mL of a 9:1 *v/v* mixture) was flushed, at 22 °C, with nitrogen for 0.25 h then heated under reflux for 3 h before being cooled, quenched with water (50.0 mL) and extracted with ethyl acetate (3 × 50.0 mL). The combined organic layers were washed with brine (1 × 50.0 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica gel, 9:1→ 4:1 *v/v* hexane/ethyl acetate) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 7:3 *v/v* hexane/ethyl acetate), compound **3.11** (2.07 g, 83%) as white, crystalline solid, m.p. = 161-163 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.40 (d, J = 8.0 Hz, 2H), 7.18 (s, 1H), 7.05 (d, J = 8.0 Hz, 2H), 6.38 (s, 1H), 6.04-5.96 (complex m, 3H), 5.36 (t, J = 3.4 Hz, 1H), 4.20 (m, 1H), 4.13 (m, 1H), 3.79 (s, 3H), 2.37 (s, 3H), 2.32 (m, 1H), 2.19 (m, 1H), 2.10-1.99 (complex m, 2H), 0.94 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 166.9, 150.2, 146.6, 142.4, 139.6, 138.4, 129.1, 126.9, 124.0, 122.4, 111.6, 109.9, 101.9, 66.1, 52.2, 51.2, 37.2, 34.4, 26.1, 21.6, 18.2, –4.6, –4.7 (five signal obscured or overlapping);

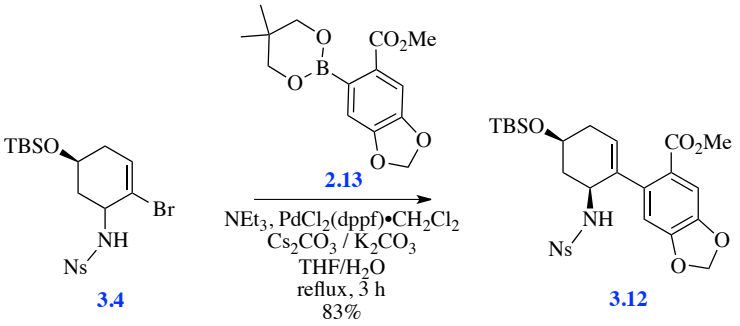
IR (KBr) ν_{max} 3361, 2953, 2927, 2856, 1714, 1614, 1505, 1485, 1435, 1371, 1335, 1252,

1157, 1124, 1092, 1038, 836 cm^{-1};

MS (ESI, +ve) *m/z* 582 [$(M+Na)^+$, 100%], 560 (20);

HRMS (ESI, +ve) $(M + Na)^+$, Calculated for $C_{28}H_{37}NNaO_7SSi$: 582.1958. Found: 582.1968.

(±)-Methyl 6-((4*S*,6*S*)-*rel*-4- ((*tert*-Butyldimethylsilyl)oxy)-6-((4-nitrophenyl)sulfonamido)-cyclohex-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate [(±)-3.12]



A magnetically stirred solution of compound **3.4**[32a] (1.96 g, 4.00 mmol), compound **2.13** (1.75 g, 6.00 mmol), $PdCl_2(dppf)•CH_2Cl_2$ (164 mg, 0.220 mmol), potassium acetate (1.25 g, 12.7 mmol) and cesium carbonate (1.30 g, 4.00 mmol) in tetrahydrofuran /water (30.0 mL of a 9:1 *v/v* mixture) was degassed in a sonicator for 0.33 h and then a nitrogen atmosphere was established. The ensuing mixture was heated under reflux for 3 h before being cooled, quenched with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (1 × 150 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica gel, 10:0 → 7:3 *v/v* hexane/ethyl acetate) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 7:3 *v/v* hexane/ethyl acetate), compound **3.12** (1.94 g, 83%) as a white, crystalline solid, m.p. = 175-177 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66 (d, J = 7.9 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.45 (m, 1H), 7.09 (s, 1H), 6.58 (m, 1H), 6.31 (s, 1H), 5.88 (s, 1H), 5.86 (s, 1H), 5.40 (s, 1H), 4.49 (m, 1H), 4.23 (s, 1H), 4.13 (m, 1H), 3.85 (s, 3H), 2.36 (m, 1H), 2.27 (m, 1H), 2.19 (m, 1H), 0.95 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H);

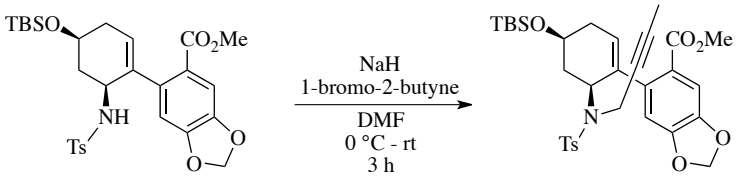
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 166.8, 149.7, 147.0, 146.6, 138.8, 135.6, 132.5, 131.9, 129.7, 124.8, 124.6, 122.7, 110.8, 109.7, 101.7, 65.9, 53.1, 52.3, 39.3, 34.7, 26.0, 18.3, –4.7, –4.7 (three signals obscured or overlapping);

IR (KBr) ν_{max} 3374, 2928, 2856, 1712, 1541, 1486, 1437, 1407, 1368, 1253, 1165, 1124, 1038, 853, 836, 780 cm^{-1};

MS (ESI, +ve) *m/z* 613 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) $(M+Na)^+$, Calculated for $C_{27}H_{34}N_2NaO_9SSi$: 613.1652. Found: 613.1652.

(±)-Methyl 6-((4*S*,6*S*)-6-(*N*-(But-2-yn-1-yl)-4-methylphenylsulfonamido)-4-((*tert*-butyldimethylsilyl)oxy)cyclohex-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate [(±)-3.13]



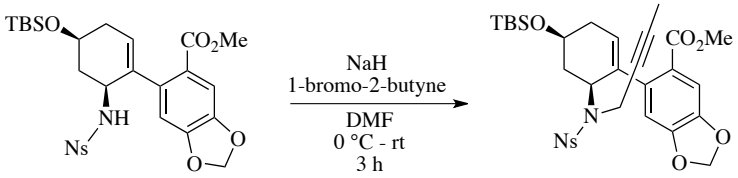
3.11 3.13

A magnetically stirred solution of compound **3.11** (2.30 g, 4.11 mmol) in *N*,*N*-dimethylformamide (30.0 mL) maintained under a nitrogen atmosphere at 0 °C was treated with sodium hydride (197 mg of a 60% suspension in oil, 4.93 mmol). After 0.33 h the reaction mixture was treated with 1-bromobut-2-yne[68] (720 μL, 8.22 mmol) and the mixture thus obtained allowed to warm to 22 °C, stirred at this temperature for 3 h then quenched with water (40.0 mL) (CAUTION: possibility for evolution of hydrogen gas) before being diluted with ethyl acetate (50.0 mL). The separated aqueous layer was extracted with ethyl acetate (3 × 20.0 mL) and the combined organic layers washed with water (5 × 20.0 mL) then brine (1 × 40.0 mL) before being dried ($MgSO_4$), filtered and

concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica gel, 9:1 → 4:1 *v*/*v* hexane/ethyl acetate) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 7:3 *v*/*v* hexane/ethyl acetate), compound **3.13** (2.24 g, 89%) as a white, crystalline solid, m.p. = 172-174 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (d, J = 8.2 Hz, 2H), 7.33 (s, 1H), 7.19 (d, J = 8.2 Hz, 2H), 6.66 (s, 1H), 6.01 (s, 2H), 5.64 (m, 1H), 5.20 (m, 1H), 3.93 (m, 2H), 3.84 (s, 3H), 3.73 (m, 1H), 2.40 (s, 3H), 2.37 (m, 1H), 2.09 (m, 1H), 1.97 (m, 1H), 1.76 (m, 1H), 1.64 (t, J = 2.3 Hz, 3H), 0.85 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 166.8, 150.2, 146.7, 142.9, 139.9, 138.3, 138.0, 129.1, 128.8, 127.9, 123.0, 111.0, 110.4, 102.0, 80.7, 75.3, 67.2, 57.3, 52.1, 37.2, 35.8, 34.2, 26.0, 21.6, 18.2, 3.6, –4.4, –4.5 (four signals obscured or overlapping);
IR (KBr) ν_{max} 2953, 2928, 2856, 1721, 1612, 1505, 1486, 1435, 1367, 1339, 1248, 1163, 1123, 1104, 1091, 1036, 836 cm^{-1};
MS (ESI, +ve) *m/z* 634 [$(M+Na)^+$, 100%];
HRMS (ESI, +ve) $(M + Na)^+$, Calculated for $C_{32}H_{41}NNaO_7SSi$: 634.2271. Found: 634.2272.

(±)-Methyl 6-((4*S*,6*S*)-6-(*N*-(But-2-yn-1-yl)-2-nitrophenylsulfonamido)-4-((*tert*-butyldimethylsilyl)oxy)cyclohex-1-en-1-yl)benzo[*d*][1,3]dioxole-5-carboxylate [(±)-3.14]



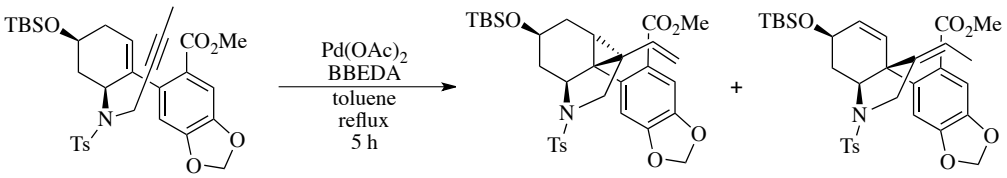
3.12 3.14

A magnetically stirred solution of compound **3.12** (3.29 g, 5.57 mmol) in *N*,*N*-dimethylformamide (50.0 mL) maintained under a nitrogen atmosphere at 0 °C was treated with sodium hydride (267 mg of a 60% suspension in oil, 6.68 mmol). After 0.33 h the reaction mixture was treated with 1-bromobut-2-yne (976 μL, 11.1 mmol). The mixture

thus obtained was allowed to warm to 22 °C then heated to 60 °C and stirred at this temperature for 3 h before being cooled then quenched with ice-water (40.0 mL) (CAUTION: possibility for evolution of hydrogen gas) and diluted with ethyl acetate (50.0 mL). The separated aqueous layer was extracted with ethyl acetate (3 × 50.0 mL) and the combined organic layers washed with water (5 × 40.0 mL) then brine (1 × 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica gel, 10:0 → 7:3 *v/v* hexane/ethyl acetate) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 7:3 *v/v* hexane/ethyl acetate), compound **3.14** (3.33 g, 93%) as a light-yellow solid, m.p. = 189-191 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.02 (d, J = 7.9 Hz, 1H), 7.61 (m, 1H), 7.52 (m, 1H), 7.49 (dd, J = 7.9 and 1.4 Hz, 1H), 7.22 (s, 1H), 6.61 (s, 1H), 5.96 (s, 2H), 5.66 (m, 1H), 5.30 (m, 1H), 4.14-4.01 (complex m, 2H), 3.86 (broad s, 1H), 3.80 (s, 3H), 2.42 (m, 1H), 2.24-2.06 (complex m, 3H), 1.61 (s, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 166.6, 150.2, 148.1, 146.7, 139.0, 137.4, 133.9, 133.3, 131.7, 130.8, 129.5, 123.5, 123.0, 110.8, 110.2, 101.9, 81.2, 75.1, 67.0, 58.3, 52.0, 37.8, 35.8, 34.6, 25.9, 18.1, 3.5, –4.5, –4.5 (two signals obscured or overlapping);
IR (KBr) ν_{max} 2953, 2929, 2895, 2856, 1720, 1545, 1485, 1436, 1371, 1249, 1169, 1123, 1102, 1035, 861, 836, 777 cm^{-1};
MS (ESI, +ve) *m/z* 665 [$(M+Na)^+$, 100%];
HRMS (ESI, +ve) $(M+Na)^+$, Calculated for $C_{31}H_{38}N_2NaO_9SSi$: 665.1964. Found: 665.1965.

(±)-Methyl 6-((2a^1*R*,2b*S*,4*S*,5a*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-tosyl-2a-vinyloctahydro-1*H*-cyclopropa[*cd*]indol-2a^1-yl)benzo[*d*][1,3]dioxole-5-carboxylate [(±)-3.15] and (±)-Methyl 6-((3a*R*,6*R*,7a*S*,*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-ethylidene-1-tosyl-2,3,3a,6,7,7a-hexahydro-1*H*-indol-3a-yl)benzo[*d*][1,3]dioxole-5-carboxylate [(±)-3.16]



3.13 → 3.15 (38%) + 3.16 (47%)

A magnetically stirred solution of compound **3.13** (1.56 g, 2.55 mmol) in toluene (40.0 mL) containing $Pd(OAc)_2$ (115 mg, 0.510 mmol) and BBEDA (125 mg, 0.510 mmol) was flushed with nitrogen for 0.25 h then heated under reflux 5 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica gel, 9:1 → 4:1 *v/v* hexane/ethyl acetate) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.8 in 7:3 *v/v* hexane/ethyl acetate) gave compound **3.15** (592 mg, 38%) as white, crystalline solid, m.p. = 171-173 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.84 (d, *J* = 8.3 Hz, 2H), 7.37 (s, 1H), 7.26 (partially obscured d, *J* = 8.3 Hz, 2H), 6.65 (s, 1H), 6.02 (s, 2H), 5.07 (m, 1H), 4.84 (s, 1H), 4.81 (d, *J* = 6.8 Hz, 1H), 4.44 (broad s, 1H), 4.12 (m, 1H), 4.09 (d, *J* = 8.8 Hz, 1H), 3.72 (s, 3H), 3.25 (d, *J* = 8.8 Hz, 1H), 2.40 (s, 3H), 2.25 (dd, *J* = 15.5 and 4.3 Hz, 1H), 2.11-1.96 (complex m, 2H), 1.46-1.33 (complex m, 2H), 0.92 (s, 9H), 0.09 (s, 6H);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 165.9, 150.6, 147.0, 142.8, 136.9, 136.6, 134.2, 129.3, 127.9, 125.3, 113.7, 112.3, 111.1, 102.0, 66.6, 63.2, 52.4, 50.3, 41.5, 39.5, 34.7, 27.0, 25.9, 25.2, 21.5, 18.1, –4.5, –4.6 (four signals obscured or overlapping);
IR (KBr) ν_{max} 2952, 2856, 1729, 1616, 1505, 1488, 1435, 1378, 1338, 1257, 1162, 1098, 1037, 932, 836, 777, 662 cm^{-1};

MS (ESI, +ve) *m/z* 634 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) $(M + Na)^+$, calculated for $C_{32}H_{41}NNaO_7SSi$: 634.2271. Found: 634.2272.

Concentration of fraction B (R_f = 0.7 in 7:3 *v/v* hexane/ethyl acetate) gave compound **3.16** (730 mg, 47%) as white, crystalline solid, m.p. = 165-167 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.45 (d, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 6.71 (s, 1H), 6.10 (s, 1H), 5.94 (d, *J* = 1.3 Hz, 1H), 5.81 (d, *J* = 1.3 Hz, 1H), 5.62 (d, *J* = 10.1 Hz, 1H), 5.46 (dd, *J* = 10.1 and 2.1 Hz, 1H), 5.35 (m, 1H), 5.12 (dd, *J* = 12.4 and 4.7 Hz, 1H), 4.57 (m, 1H), 4.34 (d, *J* = 14.8 Hz, 1H), 4.00 (d, *J* = 14.8 Hz, 1H), 3.73 (s, 3H), 2.33 (m, 1H), 2.32 (s, 3H), 1.71-1.60 (complex m, 4H), 0.92 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H);

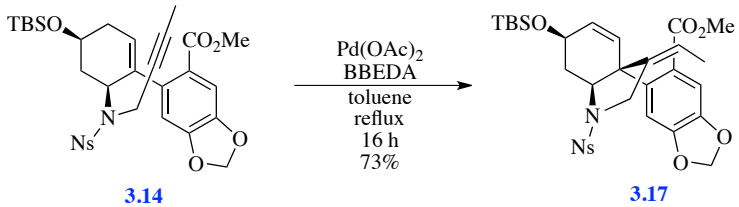
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.4, 148.2, 145.8, 142.3, 141.9, 138.3, 136.0, 132.4, 129.1, 129.0, 126.8, 126.7, 123.2, 109.5, 109.1, 101.7, 67.4, 65.2, 54.3, 52.5, 48.9, 39.7, 26.1, 21.4, 18.4, 14.9, –4.4, –4.6 (four signals obscured or overlapping);

IR (KBr) ν_{max} 2952, 2928, 2857, 1725, 1619, 1599, 1506, 1487, 1434, 1346, 1246, 1159, 1084, 1040, 932, 875, 835, 779, 665 cm^{-1};

MS (ESI, +ve) *m/z* 634 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) $(M + Na)^+$, calculated for $C_{32}H_{41}NNaO_7SSi$: 634.2271. Found: 634.2272.

(±)-Methyl 6-((3a*R*,6*R*,7a*S*,*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-ethylidene-1-((2-nitrophenyl)sulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indol-3a-yl)benzo[*d*][1,3]dioxole-5-carboxylate [(±)-3.17]

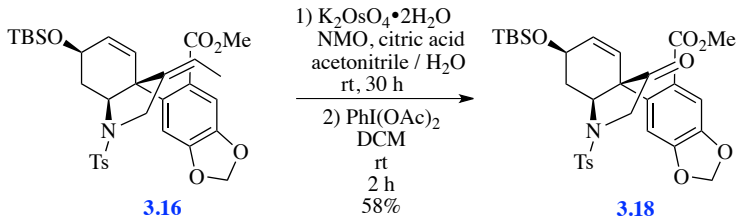


3.14 3.17

A magnetically stirred solution of compound **3.14** (500 mg, 0.780 mmol) in toluene (10.0 mL) containing $Pd(OAc)_2$ (35.0 mg, 0.160 mmol) and BBEDA (38.0 mg, 0.160 mmol) was degased in a sonicator for 0.5 h then heated under reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica gel, 10:0 → 7:3 *v/v* hexane/ethyl acetate) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 7:3 *v/v* hexane/ethyl acetate), compound **3.17** (370 mg, 73%) as a light-yellow solid, m.p. = 175-177 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (d, J = 8.1 Hz, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 6.63 (s, 1H), 6.45 (s, 1H), 5.85 (s, 1H), 5.80 (s, 1H), 5.65 (d, J = 10.2 Hz, 1H), 5.55 (d, J = 10.2 Hz, 1H), 5.37 (m, 1H), 5.13 (m, 1H), 4.65 (d, J = 15.6 Hz, 1H), 4.63-4.55 (complex m, 1H), 4.34 (d, J = 15.6 Hz, 1H), 3.73 (s, 3H), 2.31 (m, 1H), 1.74 (m, 3H), 1.54 (s, 1H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.7, 147.9, 147.4, 145.9, 141.9, 137.9, 132.9, 132.4, 132.1, 131.3, 130.0, 128.9, 126.7, 123.1, 122.9, 109.7, 109.1, 101.7, 67.3, 65.8, 54.3, 52.6, 48.8, 38.5, 26.1, 18.4, 15.0, –4.4, –4.6 (two signals obscured or overlapping);
IR (KBr) ν_{max} 2952, 2929, 2857, 1722, 1543, 1487, 1435, 1371, 1356, 1247, 1164, 1119, 1071, 1040, 909, 852, 835, 776, 728 cm^{-1};
MS (ESI, +ve) *m/z* 665 [$(M+Na)^+$, 100%];
HRMS (ESI, +ve) $(M+Na)^+$, calculated for $C_{31}H_{38}N_2NaO_9SSi$: 665.1967. Found: 665.1965.

(±)-Methyl 6-((3a*S*,6*R*,7a*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-oxo-1-tosyl-2,3,3a,6,7,7a-hexahydro-1*H*-indol-3a-yl)benzo[*d*][1,3]dioxole-5-carboxylate [(±)-3.18]



3.16 3.18

Step i: A magnetically stirred solution of compound **3.16** (400 mg, 0.650 mmol) in

acetonitrile/water (5.00 mL of a 4:1 *v/v* mixture) maintained at 22 °C was treated with citric acid (379 mg, 1.95 mmol), *N*-methylmorpholine *N*-oxide (235 mg, 1.37 mmol) and potassium osmate dihydrate (25.1 mg, 0.0670 mmol).[69] The ensuing mixture, which developed a green coloration within a few minutes, was stirred vigorously at 22 °C for 30 h then diluted with ethyl acetate (10 mL) and hydrochloric acid(10 mL of a 1 M aqueous solution). The separated aqueous phase was extracted with ethyl acetate (2 × 10.0 mL) and the combined organic phases were washed with brine (1 × 20.0 mL) then dried (MgSO4), filtered and concentrated under reduced pressure. The resulting light-brown oil was dissolved in a minimum volume of dichloromethane and the resulting solution treated with TLC-grade silica gel (100 mg) before being concentrated under reduced pressure. The free-flowing solid thus obtained was loaded onto the top of a short plug of TLC-grade silica gel that was then rinsed with hexane/ethyl acetate (200 mL of a 2:1 *v/v* mixture). The filtrate was concentrated under reduced pressure and the crude diol (now free from osmium-containing impurities) was subjected to *step ii* of the reaction sequence as described immediately below.

Step ii: The crude diol obtained as described above was dissolved in dichloromethane (5.00 mL) and the solution thus obtained treated with iodobenzene diacetate (240 mg, 0.750 mmol). The ensuing mixture was vigorously stirred at 22 °C for 2 h then treated with TLC-grade silica (100 mg) and concentrated under reduced pressure. The resulting free-flowing solid was subject to flash chromatography (silica, dry loading, 9:1 → 7:3 *v/v* hexane/ethyl acetate) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 7:3 *v/v* hexane/ethyl acetate), compound **3.18** (226 mg, 58%) as a white glass.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.57 (d, J = 8.2 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 6.61 (s, 1H), 6.24 (dd, J = 10.0, 4.6 Hz, 1H), 5.84 (s, 2H), 5.20 (d, J = 10.0 Hz, 1H), 5.12 (s, 1H), 4.23 (t, J = 4.8 Hz, 1H), 4.03 (s, 1H), 3.88-3.74 (complex m, 2H), 3.13 (s, 1H), 2.87 (dd, J = 15.2, 3.6 Hz, 1H), 2.22 (s, 2H), 1.51-1.43 (complex m, 1H), 1.10 (s, 3H), 0.82 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H);

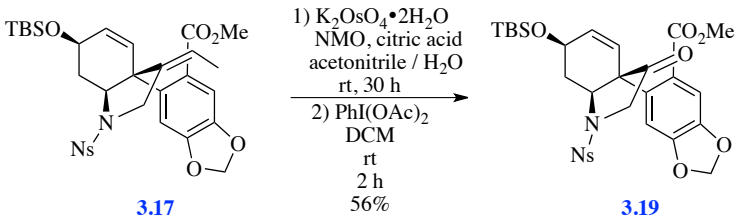
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 204.8, 166.0, 151.4, 147.2, 142.8, 136.3, 135.6, 134.5, 129.3, 128.5, 126.0, 120.6, 111.8, 111.7, 102.4, 62.0, 61.7, 60.1, 55.0, 53.5, 51.7, 31.3, 26.2, 18.5, –4.5, –4.6 (four signals obscured or overlapping);

IR (KBr) ν_{max} 2926, 1755, 1714, 1541, 1487, 1437, 1369, 1356, 1247, 1164, 1119, 1071, 1040, 909, 852, 835, 776, 728 cm^{-1};

MS (ESI, +ve) *m/z* 600 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) $(M+H)^+$, calculated for $C_{30}H_{38}NO_8SSi$: 600.2087. Found: 600.2090.

(±)-Methyl 6-((3a*S*,6*R*,7a*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-((2-nitrophenyl)sulfonyl)-3-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indol-3a-yl)benzo[*d*][1,3]dioxole-5-carboxylate [(±)-3.19]



3.17 3.19

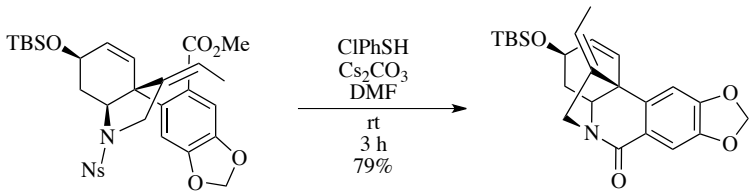
Step i: A magnetically stirred solution of compound **3.17** (325 mg, 0.510 mmol) in acetonitrile/water (5 mL of a 4:1 *v/v* mixture) maintained at 22 °C was treated with citric acid (297 mg, 1.53 mmol), *N*-methylmorpholine *N*-oxide (190 mg, 1.00 mmol) and potassium osmate dihydrate (19.5 mg, 0.0520 mmol). The ensuing mixture, which developed a green coloration within a few minutes, was stirred vigorously at 22 °C for 30 h then diluted with ethyl acetate (10.0 mL) and hydrochloric acid (10.0 mL of a 1 M aqueous solution). The separated aqueous phase was extracted with ethyl acetate (2 × 10.0 mL) and the combined organic phases were washed with brine (1 × 20.0 mL) then dried (MgSO4), filtered and concentrated under reduced pressure. The resulting light-brown oil was dissolved in a minimum volume of dichloromethane and the resulting solution treated with TLC-grade silica gel (100 mg) before being concentrated under reduced pressure. The free-flowing solid thus obtained was loaded onto the top of a short plug of TLC-grade silica gel that was then rinsed with hexane/ethyl acetate (200 mL of a 1:2 *v/v* mixture). The filtrate

was concentrated under reduced pressure and the crude diol (now free from osmium-containing impurities) was subjected to *step ii* of the reaction sequence as described immediately below.

Step ii: The crude diol obtained as described above was dissolved in dichloromethane (5.00 mL) and the solution thus obtained treated with iodobenzene diacetate (190 mg, 0.590 mmol). The ensuing mixture was vigorously stirred at 22 °C for 2 h then treated with TLC-grade silica (100 mg) and concentrated under reduced pressure. The resulting free-flowing solid was subject to flash chromatography (silica, dry loading, 9:1 → 7:3 *v/v* hexane/ethyl acetate) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 7:3 *v/v* hexane/ethyl acetate), compound **3.19** (186 mg, 56%) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.05 (m, 1H), 7.64 (m, 2H), 7.54-7.48 (complex m, 1H), 7.44 (d, J = 0.7 Hz, 1H), 6.80 (d, J = 0.7 Hz, 1H), 6.43 (dd, J = 10.0, 5.0 Hz, 1H), 6.03 (m, 2H), 5.43 (m, 1H), 4.72 (t, J = 3.5 Hz, 1H), 4.38 (t, J = 4.9 Hz, 1H), 4.17 (m, 2H), 3.25 (s, 3H), 2.89 (d, J = 14.7 Hz, 1H), 1.69-1.62 (complex m, 1H), 0.95 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 204.0, 166.6, 151.6, 149.1, 147.3, 136.2, 135.9, 132.9, 132.0, 131.5, 130.9, 126.2, 123.6, 120.5, 111.9, 111.7, 102.5, 62.0, 61.9, 59.8, 54.7, 52.0, 31.3, 26.2, 18.5, –4.5, –4.7 (two signals obscured or overlapping);
IR (KBr) ν_{max} 2928, 2855, 1958, 1755, 1710, 1617, 1546, 1507, 1489, 1436, 1365, 1258, 1170, 1082, 837, 776, 593 cm^{-1};
MS (ESI, +ve) *m/z* 632 [$(M+H)^+$, 100%];
HRMS (ESI, +ve) $(M+H)^+$, calculated for $C_{29}H_{35}N_2O_{10}SSi$: 631.1782. Found: 631.1782.

(±)-(3*R*,5*S*,11b*R*,*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-12-ethylidene-4,4a-dihydro-5,11b-ethano[1,3]dioxolo[4,5-*j*]phenanthridin-6(3*H*)-one [(±)-3.20]



3.17 3.20

A magnetically stirred solution of compound **3.17** (224 mg, 0.350 mmol) in dry *N*,*N*-dimethylformamide (10.0 mL) containing cesium carbonate (516 mg, 1.58 mmol) and 4-chlorothiophenol (211 mg, 1.46 mmol) was stirred at 22 °C for 1 h then quenched with NH_4Cl (10.0 mL of a saturated aqueous solution) and extracted with dichloromethane (3 × 20.0 mL). The combined organic layers were washed with brine (1 × 50.0 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The oily residue thus obtained was subjected to flash chromatography (silica gel, 10:0 → 4:1 *v*/*v* hexane/ethyl acetate) to afford, after concentration of the appropriate fractions (R_f = 0.7 in 4:1 *v*/*v* hexane/ethyl acetate), a white powder than upon recrystallization (methanol/dichloromethane/hexane) gave compound **3.20** (118 mg, 79%) as a white, crystalline solid, m.p. = 165-167 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44 (s, 1H), 6.81 (s, 1H), 6.32 (dd, *J* = 10.2 and 2.3 Hz, 1H), 6.00 (dd, *J* = 6.2 and 1.1 Hz, 2H), 5.80 (d, *J* = 10.2, 1H), 5.33 (m, 1H), 4.37 (m, 1H), 4.06 (d, *J* = 16.5 Hz, 1H), 3.54 (m, 2H), 1.97 (m, 1H), 1.58 (m, 1H), 1.51 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H);

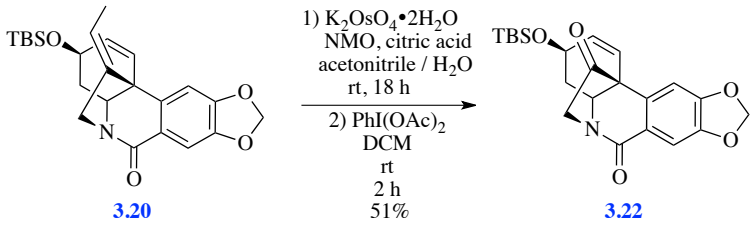
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 181.5, 152.8, 147.9, 146.7, 144.1, 134.7, 124.5, 121.6, 119.5, 110.1, 102.4, 102.1, 68.4, 68.0, 51.8, 49.2, 33.9, 26.0, 18.4, 15.3, –4.4, –4.7 (two signals obscured or overlapping);

IR (KBr) ν_{max} 2953, 2921, 2851, 1720, 1615, 1503, 1485, 1422, 1366, 1249, 1118, 1095, 1038, 932, 888, 873, 779 cm^{-1};

MS (ESI, +ve) *m/z* 426 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) $(M+H)^+$, calculated for $C_{24}H_{32}NO_4Si$: 426.2101, Found: 426.2099.

(±)- (3*R*,5*S*,11b*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-4,4a-dihydro-5,11b-ethano[1,3]dioxolo[4,5-*j*]phenanthridine-6,12(3*H*)-dione [(±)-3.22]



3.20 **3.22**

Step i: A magnetically stirred solution of compound **3.20** (800 mg, 1.86 mmol) in acetonitrile/water (100 mL of a 4:1 *v/v* mixture) maintained at 22 °C was treated with citric acid (393 mg, 2.05 mmol), *N*-methylmorpholine *N*-oxide (656 mg, 3.84 mmol) and potassium osmate dihydrate (70.0 mg, 0.190 mmol).[69] The ensuing mixture was stirred vigorously at 22 °C for 18 h before being diluted with ethyl acetate (50.0 mL) and water (50.0 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 100 mL) and the combined organic phases then washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light-brown oil was used immediately in the next step as detailed immediately below.

Step ii: A solution of the oil obtained as described above, in step i, in dichloromethane (10.0 mL) was treated with iodobenzene diacetate (663 mg, 2.05 mmol). The ensuing mixture was stirred vigorously at 22 °C for 2 h before being treated with TLC-grade silica gel (500 mg) then concentrated under reduced pressure. The resulting free-flowing solid was subjected to flash chromatography (silica gel, 10:0 → 4:1 *v/v* hexane/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.7 in 7:3 *v/v* hexane/ethyl acetate) afforded the title compound **3.22** (392 mg, 51%) as an unstable, white solid, m.p. = 105-107 °C (decompose).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.50 (s, 1H), 6.82 (s, 1H), 6.22 (d, J = 10.2 Hz, 1H), 6.06 (m, 2H), 6.00 (d, J = 10.2 Hz, 1H), 4.38 (m, 1H), 3.90 (broad d, J = 13.7 Hz, 1H), 3.81 (d, J = 18.5 Hz, 1H), 3.30 (d, J = 18.5 Hz, 1H), 2.21 (m, 1H), 1.64 (q, J = 12.2 Hz, 1H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H);

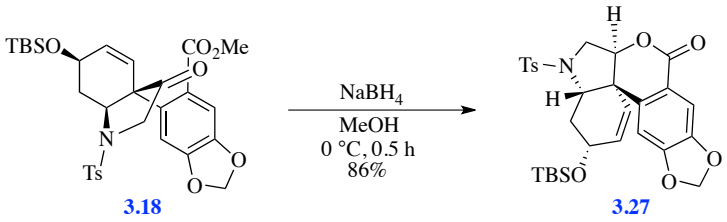
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 208.8, 179.8, 153.8, 148.1, 139.6, 138.4, 121.4, 120.3, 110.2, 104.1, 102.6, 67.7, 67.2, 53.9, 52.0, 34.4, 25.9, 18.3, –4.5, –4.7 (two signals obscured or overlapping);

IR (KBr) ν_{max} 2954, 2929, 2858, 1751, 1700, 1485, 1281, 1103, 1089, 1078, 1033, 934, 871, 851, 838, 782 cm^{-1};

MS (EI, 70 eV) *m/z* 413 ($M^{+\bullet}$, 15%), 356 (18), 329 (30), 328 (100), 298 (60), 253 (55), 225 (99);

HRMS (EI) Calculated for $C_{22}H_{27}NO_5Si$: 413.1659. Found, 413.1660.

(±)-(3*R*,4a*S*,6a*S*,13b*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-5-tosyl-4a,5,6,6a-tetrahydro-3*H*-[1,3]dioxolo[4',5':6,7]isochromeno[3,4-*c*]indol-8(4*H*)-one [(±)-3.27]

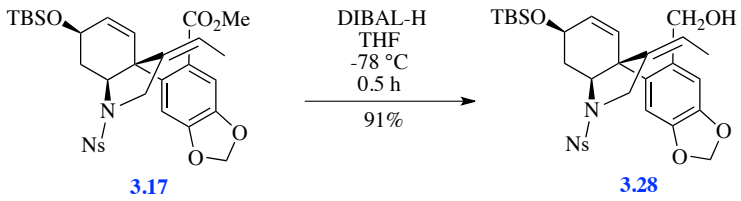


A magnetically stirred solution of compound **3.18** (100 mg, 0.170 mmol) in methanol (10.0 mL) maintained at 0 °C was treated with sodium borohydride (4.00 mg, 0.110 mmol). The ensuing mixture was stirred vigorously at 0 °C for 0.5 h before being diluted with ethyl acetate (20.0 mL) and water (10.0 mL). The seperated aqueous phase was extracted with ethyl acetate (3 × 10.0 mL) and the combined organic phase then washed with brine (1 × 10.0 mL) before being dried (MgSO4), filtered and concentrated under reduce pressure. The resulting yellow oil was subjected to flash chromatography (silica gel, 9:1 → 7:3 *v/v* hexane/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.5 in 7:3 *v/v*

hexane/ethyl acetate) afforded the title compound **3.27** (83 mg, 86%) as a white, crystalline solid, m.p. = 166-168 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.58 (d, J = 8.1 Hz, 2H), 7.35 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H), 6.45 (s, 1H), 6.08 (dd, J = 10.1, 3.7 Hz, 1H), 6.02 (dd, J = 22.3, 1.2 Hz, 2H), 5.40 (dd, J = 10.1, 1.3 Hz, 1H), 4.75 (t, J = 4.4 Hz, 1H), 4.43 (m, 1H), 3.89 (m, 2H), 3.53 (dd, J = 11.8, 4.1 Hz, 1H), 2.41 (s, 3H), 2.40-2.36 (complex m, 1H), 2.15-2.06 (complex m, 1H), 0.95 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 161.43, 152.97, 147.91, 143.83, 136.75, 135.02, 133.95, 129.62, 127.45, 126.56, 116.68, 109.91, 106.95, 102.38, 82.19, 63.69, 62.08, 52.87, 47.09, 34.50, 25.98, 21.66, 18.31, –4.48, –4.58 (four signals obscured or overlapping);
IR (KBr) ν_{max} 2929, 2853, 1715, 1507, 1438, 1349, 1277, 1056, 1039, 1016, 837, 780, 733 cm^{-1};
MS (ESI, +ve) *m/z* 571 [$(M+H)^+$, 100%];
HRMS (ESI, +ve) $(M + H)^+$, calculated for $C_{29}H_{36}NO_7SSi$: 570.1982. Found: 570.1982.

(±)-(6-((3a*R*,6*R*,7a*S*,*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-ethylidene-1-((2-nitrophenyl)sulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indol-3a-yl)benzo[*d*][1,3]dioxol-5-yl)methanol [(±)-3.28]



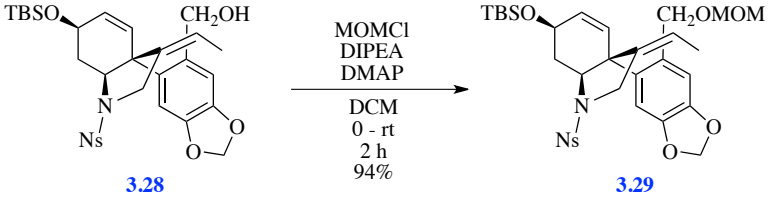
3.17 3.28

A magnetically stirred solution of compound **3.17** (500 mg, 0.780 mmol) in dry tetrahydrofuran (50.0 mL) maintained at −78 °C under a nitrogen atmosphere was treated with DIBAl-H (1.70 mL of 1.0 M solution in tetrahydrofuran, 1.70 mmol). The ensuing mixture was stirred vigorously at −78 °C for 0.5 h then quenched with tartaric acid (20.0 mL of a 1.0 M aqueous solution). The resulting mixture was stirred for 1 h and the separated aqueous layer extracted with ethyl acetate (2 × 30.0 mL). The combined organic

phase then washed with brine (1 × 10.0 mL) before being dried (MgSO4), filtered and concentrated under reduce pressure. The resulting residue was subjected to flash chromatography (silica gel, 9:1 → 7:3 *v/v* hexane/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.5 in 7:3 *v/v* hexane/ethyl acetate) afforded the title compound **3.28** (436 mg, 91%) as a white, crystalline solid, m.p. = 174-175 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.63 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.51 (td, *J* = 7.7, 1.4 Hz, 1H), 7.41-7.32 (complex m, 2H), 6.83 (s, 1H), 6.46 (s, 1H), 5.86 (d, *J* = 1.4 Hz, 1H), 5.80 (d, *J* = 1.4 Hz, 1H), 5.70 (d, *J* = 1.5 Hz, 2H), 5.51-5.43 (complex m, 1H), 4.68-4.50 (complex m, 4H), 4.38-4.24 (complex m, 2H), 2.28 (m, 1H), 1.82 (m, 1H), 1.80-1.75 (complex m, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H) (signal due to O-H group proton not observed);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 147.69, 146.82, 146.36, 141.65, 134.81, 133.55, 132.61, 132.36, 131.39, 131.37, 130.40, 129.98, 123.84, 123.45, 111.05, 109.02, 101.21, 67.62, 65.55, 62.23, 54.63, 48.64, 38.63, 26.01, 18.35, 14.95, –4.25, –4.48 (two signals obscured or overlapping);
IR (KBr) ν_{max} 2956, 2931, 2858, 1733, 1544, 1487, 1360, 1239, 1165, 1073, 1040, 932, 871, 834, 734 cm^{-1};
MS (ESI, +ve) *m/z* 637 [$(M+Na)^+$, 100%];
HRMS (ESI, +ve) $(M + Na)^+$, calculated for $C_{30}H_{38}N_2NaO_8SSi$: 637.2016. Found: 637.2016.

(±)-(3a*R*,6*R*,7a*S*,*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-ethylidene-3a-(6-((methoxymethoxy)methyl)benzo[*d*][1,3]dioxol-5-yl)-1-((4-nitrophenyl)sulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indole [(±)-3.29]



3.28 3.29

A magnetically stirred solution of compound **3.28** (200 mg, 0.330 mmol) in dry dichloromethane (10.0 mL) maintained at 0 °C under a nitrogen atmosphere was treated with di-*iso*-propylethylamine (0.10.0 mL, 0.570 mmol), chloromethyl methyl ether (0.050 mL, 0.560 mmol) followed by catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine. The ensuing mixture was stirred vigorously at 22 °C for 2 h then quenched with cold water (5.00 mL). The separated aqueous phase was extracted with dichloromethane (2 × 10.0 mL) and the combined organic phases then washed with brine (1 × 10.0 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica gel, 9:1 → 8:2 *v/v* hexane/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.7 in 7:3 *v/v* hexane/ethyl acetate) afforded the title compound **3.29** (204 mg, 94%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.52-7.41 (complex m, 2H), 7.33 (d, J = 7.9 Hz, 1H), 7.20 (t, J = 7.7 Hz, 1H), 6.77 (s, 1H), 6.46 (s, 1H), 5.83 (s, 1H), 5.78 (s, 1H), 5.68 (s, 2H), 5.47 (m, 1H), 4.75-4.56 (complex m, 5H), 4.33-4.28 (complex m, 3H), 3.49 (s, 3H), 2.35 (m, 1H), 1.83 (m, 1H), 1.78 (d, J = 7.3 Hz, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H);

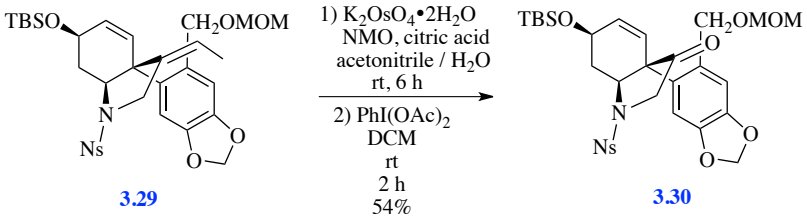
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 147.93, 146.73, 146.49, 141.60, 135.81, 132.17, 132.03, 131.38, 131.21, 130.27, 130.14, 129.96, 123.91, 122.90, 111.87, 108.76, 101.21, 96.63, 67.64, 66.60, 66.18, 56.08, 54.48, 48.06, 39.06, 26.00, 18.38, 14.93, –4.41, –4.60 (two signals obscured or overlapping);

IR (KBr) ν_{max} 2929, 2857, 2258, 1544, 1505, 1486, 1372, 1358, 1239, 1165, 1092, 1073, 1040, 914, 871, 834, 776, 729 cm^{-1};

MS (ESI, +ve) *m/z* 682 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) $(M + Na)^+$, calculated for $C_{32}H_{42}N_2NaO_9SSi$: 681.2278. Found: 681.2281.

(±)-(3a*S*,6*R*,7a*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-3a-(6-((methoxymethoxy)methyl)benzo[*d*][1,3]dioxol-5-yl)-1-((4-nitrophenyl)sulfonyl)-3a,6,7,7a-tetrahydro-1*H*-indol-3(2*H*)-one [(±)-3.30]



Step i: A magnetically stirred solution of compound **3.29** (200 mg, 0.300 mmol) in acetonitrile/water (20.0 mL of a 4:1 *v/v* mixture) maintained at 22 °C was treated with citric acid (179 mg, 0.920 mmol), *N*-methylmorpholine *N*-oxide (103 mg, 0.600 mmol) and potassium osmate dihydrate (11.3 mg, 0.030 mmol). The ensuing mixture was stirred vigorously at 22 °C for 6 h before being diluted with ethyl acetate (20.0 mL) and water (20.0 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 20 mL) and the combined organic phases then washed with brine (1 × 20.0 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting light-brown oil was used immediately in the next step as detailed immediately below.

Step ii: A solution of the oil obtained as described above, in step i, in dichloromethane (15.0 mL) was treated with iodobenzene diacetate (116 mg, 0.360 mmol). The ensuing mixture was stirred vigorously at 22 °C for 2 h before being treated with TLC-grade silica gel (200 mg) then concentrated under reduced pressure. The resulting free-flowing solid was subjected to flash chromatography (silica gel, 10:0 → 4:1 *v/v* hexane/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.6 in 7:3 *v/v* hexane/ethyl acetate) afforded the title compound **3.30** (105 mg, 54%) as white solid, m.p. = 183-185°C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.52 (m, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.31 (td, *J* = 7.7, 1.3 Hz, 1H), 6.80 (s, 1H), 6.20 (s, 1H), 5.89 (d, *J* = 10.3, 1H), 5.83 (dd, *J* = 16.2, 1.3 Hz, 2H), 5.67 (dd, *J* = 10.1, 2.1 Hz, 1H), 4.96 (dd, *J* = 12.0, 5.0 Hz, 1H), 4.71 (s, 2H), 4.62-4.52 (complex m, 3H), 4.21 (d, *J* = 11.5 Hz, 1H), 4.03 (d, *J* =

19.2 Hz, 1H), 3.50 (s, 3H), 2.46 (m, 1H), 1.79 (m, 1H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H);

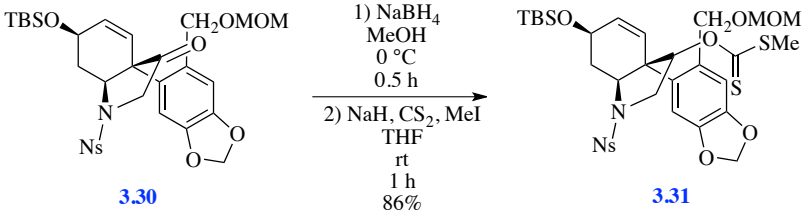
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 209.92, 147.77, 147.39, 146.85, 134.45, 132.76, 132.19, 131.81, 130.97, 130.51, 130.41, 126.81, 123.32, 112.57, 107.50, 101.59, 96.47, 66.31, 65.98, 64.41, 59.35, 56.16, 51.66, 38.46, 25.91, 18.27, –4.49, –4.67 (two signals obscured or overlapping);

IR (KBr) ν_{max} 2929, 2856, 1762, 1543, 1505, 1372, 1251, 1167, 1092, 1040, 871, 834, 782, 598 cm^{-1};

MS (ESI, +ve) *m/z* 669 [(M+Na)$^+$, 100%];

HRMS (ESI, +ve) (M + Na)$^+$, calculated for $C_{32}H_{42}N_2NaO_9SSi$: 669.1914. Found: 669.1919.

(±)-*O*-((3*S*,3a*S*,6*R*,7a*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-3a-(6-((methoxymethoxy)methyl)benzo[*d*][1,3]dioxol-5-yl)-1-((4-nitrophenyl)sulfonyl)-2,3,3a,6,7,7a-hexahydro-1*H*-indol-3-yl) *S*-methyl carbonodithioate [(±)-3.31]



3.30 3.31

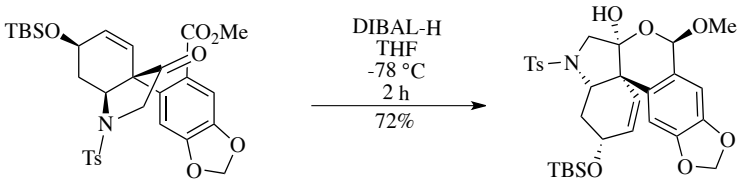
Step i: A magnetically stirred solution of compound **3.30** (100 mg, 0.150 mmol) in methanol (10.0 mL) maintained at 0 °C was treated with sodium borohydride (5.00 mg, 0.140 mmol). The ensuing mixture was stirred vigorously at 0 °C for 0.5 h before being diluted with ethyl acetate (20.0 mL) and water (10.0 mL). The seperated aqueous phase was extracted with ethyl acetate (3 × 10.0 mL) and the combined organic phase then washed with brine (1 × 10.0 mL) before being dried (MgSO4), filtered and concentrated under reduce pressure. The resulting residue was subjected to flash chromatography (silica gel, 9:1 → 7:3 *v/v* hexane/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.5 in 7:3 *v/v* hexane/ethyl acetate) afforded a clear, colourless oil. This material was

subjected, without further purification, to *step ii* of the reaction sequence as detailed immediately below.

Step ii: A solution of the oil obtained as described above, in step i, in dry tetrahydrofuran (10.0 mL) was treated with sodium hydride (5.00 mg of a 60% dispersion in mineral oil, 0.210 mmol) and stirred at 22 °C for 0.17 h. Carbon disulphide (0.120 mL, 2.00 mmol) was then added to the reaction mixture and refluxed for 0.5 h. The reaction mixture was allowed to cool to 22 °C and methyl iodide (0.0500 mL, 0.790 mmol) was added after and stirred vigorously for another 0.5 h. The reaction mixture was cooled to 0 °C, quenched with iced water (5.00 mL) (CAUTION! EXOTHERMIC REACTION), and then diluted with ethyl acetate (10.0 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 10.0 mL) and the combined organic phase dried with $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography (silica gel, 10:0 → 4:1 *v/v* hexane/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.7 in 7:3 *v/v* hexane/ethyl acetate) afforded the title compound **3.31** (95.0 mg, 86%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.88 (d, J = 7.0 Hz, 1H), 7.57 (m, 2H), 7.48 (m, 1H), 6.90 (s, 1H), 6.87 (s, 1H), 6.03 (d, J = 10.4 Hz, 1H), 5.99-5.89 (complex m, 3H), 5.12 (s, 1H), 4.60 (s, 2H), 4.57 (d, J = 12.1 Hz, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.35 (t, J = 7.1 Hz, 1H), 4.28 (m, 1H), 4.14 (d, J = 13.2 Hz, 1H), 4.03 (m, 1H), 3.38 (s, 3H), 2.69 (m, 1H), 2.50 (t, J = 8.2 Hz, 1H), 1.86 (s, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 213.67, 148.50, 147.33, 146.45, 133.08, 133.01, 131.77, 131.61, 130.83, 130.78, 129.73, 127.59, 123.47, 112.08, 108.19, 101.46, 95.48, 86.24, 68.48, 67.27, 62.63, 59.99, 55.71, 53.85, 51.64, 34.18, 25.89, 18.22, –4.69, –4.80 (two signals obscured or overlapping);
IR (KBr) ν_{max} 2930, 2893, 2859, 1546, 1508, 1489, 1372, 1210, 1168, 1073, 1035, 836, 776 cm^{-1};
MS (ESI, +ve) *m/z* 762 [$(M+Na)^+$, 100%];
HRMS (ESI, +ve) $(M + Na)^+$, calculated for $C_{32}H_{42}N_2NaO_{10}S_3Si$: 761.1669. Found: 761.1670.

(±)-(3*R*,4a*S*,6a*S*,8*R*,13b*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-8-methoxy-5-tosyl-4,4a,5,6,6a,8-hexahydro-3*H*-[1,3]dioxolo[4',5':6,7]isochromeno[3,4-*c*]indol-6a-ol [(±)-3.43]



3.18 3.43

A magnetically stirred solution of compound **3.18** (100 mg, 0.170 mmol) in dry tetrahydrofuran (20.0 mL) maintained at −78 °C under a nitrogen atmosphere was treated with DIBAl-H (0.300 mL of 1.0 M solution in tetrahydrofuran, 0.300 mmol). The ensuing mixture was stirred vigorously at −78 °C for 2 h then quenched with tartaric acid (10.0 mL of a 1.0 M aqueous solution). The resulting mixture was stirred for 1 h and the separated aqueous layer extracted with ethyl acetate (2 × 30.0 mL). The combined organic phase then washed with brine (1 × 10.0 mL) before being dried (MgSO4), filtered and concentrated under reduce pressure. The resulting residue was subjected to flash chromatography (silica gel, 9:1 → 7:3 *v/v* hexane/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.6 in 7:3 *v/v* hexane/ethyl acetate) afforded the title compound **3.43** (74.0 mg, 72%) as a white solid, m.p. = 182-183 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44 (d, J = 8.2 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.42 (s, 1H), 6.16 (s, 1H), 6.02 (d, J = 10.1, 1H), 5.99 (d, J = 1.3 Hz, 1H), 5.83 (d, J = 1.3 Hz, 1H), 5.38 (s, 1H), 5.24 (dd, J = 10.0, 1.9 Hz, 1H), 4.45 (m, 1H), 4.12 (dd, J = 10.7, 1.7 Hz, 1H), 4.03 (dd, J = 11.6, 5.2 Hz, 1H), 3.67 (d, J = 10.7 Hz, 1H), 3.47 (s, 3H), 3.04 (d, J = 1.7 Hz, 1H), 2.48-2.42 (complex m, 1H), 2.35 (s, 3H), 2.32-2.23 (complex m, 1H), 0.93 (s, 9H), 0.14 (s, 6H);

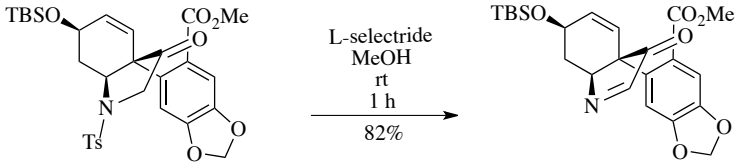
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 148.22, 147.20, 142.92, 138.79, 133.91, 130.48, 129.20, 127.55, 125.44, 124.40, 107.04, 106.67, 101.47, 101.35, 98.63, 66.66, 63.84, 55.88, 55.03, 50.67, 38.32, 26.01, 21.49, 18.34, –4.26, –4.5 (four signals obscured or overlapping);

IR (KBr) ν_{max} 3434, 2926, 1486, 1343, 1243, 1155, 1092, 1031, 932, 872, 835, 777, 662, 548 cm^{-1};

MS (ESI, +ve) *m/z* 624 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) $(M + Na)^+$, calculated for $C_{30}H_{39}NNaO_8SSi$: 624.2063. Found: 624.2064.

(±)-Methyl 6-((3a*S*,6*R*,7a*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-oxo-3a,6,7,7a-tetrahydro-3*H*-indol-3a-yl)benzo[*d*][1,3]dioxole-5-carboxylate [(±)-3.44]



3.18 3.44

A magnetically stirred solution of compound **3.18** (100 mg, 0.170 mmol) in dry methanol (10.0 mL) maintained at 22 °C under a nitrogen atmosphere was treated with L-selectride (0.200 mL of 1.0 M solution in tetrahydrofuran, 0.200 mmol). The ensuing mixture was stirred vigorously at 22 °C for 1 h before being diluted with ethyl acetate (10.0 mL) and water (10.0 mL). The seperated aqueous phase was extracted with ethyl acetate (3 × 10.0 mL) and the combined organic phase then washed with brine (1 × 10.0 mL) before being dried (MgSO4), filtered and concentrated under reduce pressure. The resulting residue was subjected to flash chromatography (silica gel, 10:0 → 4:1 *v/v* hexane/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.8 in 7:3 *v/v* hexane/ethyl acetate) afforded the title compound **3.44** (62.0 mg, 82%) as a white solid, m.p. = 175-177 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 (d, *J* = 3.1 Hz, 1H), 7.46 (s, 1H), 6.92 (s, 1H), 6.12 (ddd, *J* = 9.9, 5.3, 1.1 Hz, 1H), 6.04 (s, 2H), 5.42 (d, *J* = 9.9, 1H), 4.67 (m, 1H), 4.28 (m, 1H), 3.71 (s, 3H), 2.59 (m, 1H), 2.01 (dt, *J* = 15.0, 4.8 Hz, 1H), 0.89 (s, 9H), 0.10 (s, 3H), 0.04 (s, 3H);

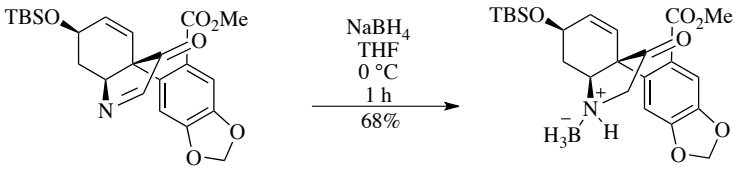
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 200.25, 167.19, 160.76, 151.30, 146.85, 135.82, 133.57, 127.39, 121.74, 112.08, 111.60, 102.33, 73.78, 62.19, 56.02, 52.38, 31.97, 25.88, 18.21, –4.40, –4.55 (two signals obscured or overlapping);

IR (KBr) ν_{max} 2953, 2928, 2856, 1737, 1714, 1617, 1506, 1488, 1436, 1363, 1250, 1116, 1073, 1037, 835, 775 cm^{-1};

MS (ESI, +ve) *m/z* 466 [$(M+Na)^+$, 100%];

HRMS (ESI, +ve) $(M + H)^+$, calculated for $C_{23}H_{29}NNaO_6Si$: 466.1662. Found: 466.1663.

(±)-((1*R*,3a*S*,6*R*,7a*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-3a-(6-(methoxycarbonyl)benzo[*d*][1,3]dioxol-5-yl)-3-oxo-2,3,3a,6,7,7a-hexahydro-1*H*-indol-1-ium-1-yl)trihydroborate [(±)-3.45]



3.44 3.45

A magnetically stirred solution of compound **3.44** (50.0 mg, 0.110 mmol) in tetrahydrofuran (10.0 mL) maintained at 0 °C was treated with sodium borohydride (4.00 mg, 0.110 mmol). The ensuing mixture was stirred vigorously at 0 °C for 1 h before being diluted with ethyl acetate (10.0 mL) and water (10.0 mL). The seperated aqueous phase was extracted with ethyl acetate (3 × 10.0 mL) and the combined organic phase then washed with brine (1 × 10.0 mL) before being dried (MgSO4), filtered and concentrated under reduce pressure. The resulting brown oil was subjected to flash chromatography (silica gel, 19:1 *v/v* dichloromethane/ammonia-saturated methanol) and concentration of the appropriate fractions (R_f = 0.9 in 9:1 *v/v* dichloromethane/ammonia-saturated methanol) afforded the title compound **3.45** (34.0 mg, 68%) as a white, crystalline solid, m.p. = 102 °C (decompose).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.53 (s, 1H), 6.79 (s, 1H), 6.48-6.38 (complex m, 2H), 6.04 (s, 2H), 5.52 (dd, *J* = 9.9, 1.7 Hz, 1H), 4.39 (t, *J* = 4.8 Hz, 1H), 4.11 (m, 1H), 3.97 (dd,

J = 18.0, 8.7 Hz, 1H), 3.84 (s, 3H), 3.72 (dd, J = 18.0, 8.6 Hz, 1H), 2.70 (m, 1H), 1.65-1.58 (complex m, 1H), 0.94 (s, 9H), 0.21 (s, 3H), 0.16 (s, 3H);

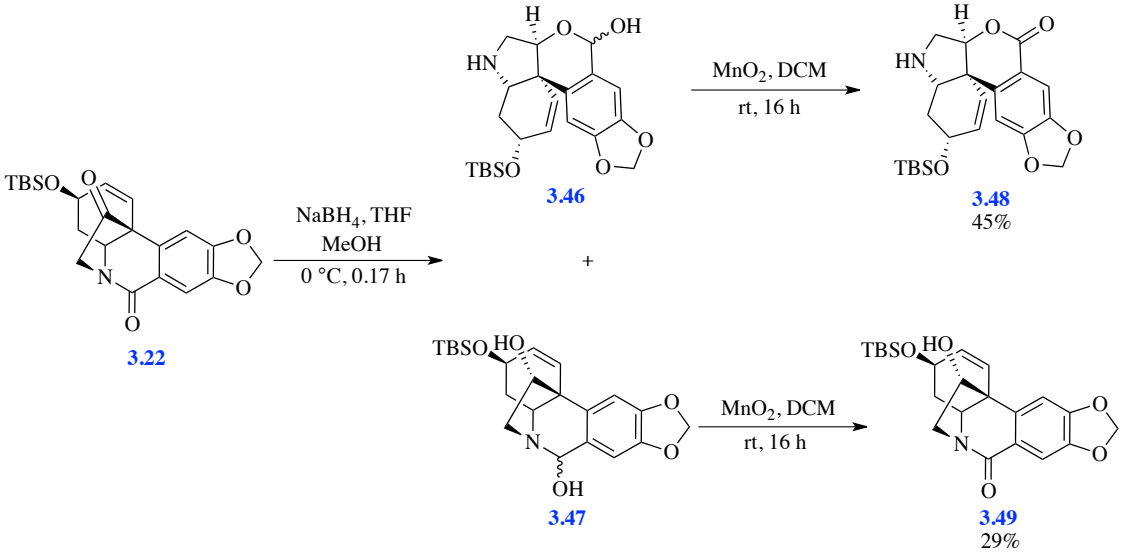
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 206.64, 166.99, 151.37, 147.39, 134.09, 134.07, 126.90, 121.62, 111.97, 111.63, 102.53, 66.79, 62.66, 59.63, 59.60, 52.79, 26.11, 25.91, 18.18, –4.75, –4.79 (two signals obscured or overlapping);

IR (KBr) ν_{max} 3427, 2952, 2856, 1714, 1618, 1505, 1488, 1436, 1358, 1250, 1119, 1067, 1034, 836, 840, 779 cm^{-1};

MS (ESI, +ve) *m/z* 482 [(M + Na)$^+$, 28%], 446 (100%);

HRMS (ESI, +ve) (M + Na)$^+$, calculated for $C_{23}H_{34}BNNaO_6Si$: 482.2146. Found: 482.2147.

(±)-(3*R*,4a*S*,6a*S*,13b*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-4a,5,6,6a-tetrahydro-3*H*-[1,3]dioxolo[4',5':6,7]isochromeno[3,4-*c*]indol-8(4*H*)-one [(±)-3.48] and (±)-(3*R*,5*S*,11b*S*,12*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-12-hydroxy-4,4a-dihydro-11b,5-ethano[1,3]dioxolo[4,5-*j*]phenanthridin-6(3*H*)-one [(±)-3.49]



Step i: A magnetically stirred solution of compound **3.22** (240 mg, 0.580 mmol) in tetrahydrofuran was cooled to 0 °C then treated with chilled methanol (10.0 mL) followed by sodium borohydride (219 mg, 5.80 mmol). The ensuing mixture was warmed to 22 °C then stirred at this temperature for 0.25 h before being quenched with NH_4Cl (5.00 mL of a

saturated aqueous solution) then diluted with ethyl acetate (30.0 mL) and water (30.0 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 30.0 mL) and the combined organic phases then washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing light-brown oil was subjected to flash chromatography (silica gel, 10:0 → 95:5 *v/v* dichloromethane/ammonia-saturated methanol) and concentration of the appropriate fractions (R_f = 0.5 in 95:5 *v/v* dichloromethane/ammonia-saturated methanol) afforded a *ca*. 3:2 mixture of compounds **3.46** and **3.47** (181 mg) as a clear, colourless oil.

Step ii: A vigorously stirred solution of a *ca*. 3:2 mixture of compounds **3.46** and **3.47** (181 mg, 0.430 mmol) in dichloromethane (20.0 mL) was treated with manganese (IV) oxide (377 mg) and the ensuing mixture mainatined at 22 °C for 16 h then filtered through a pad of diatomaceous earth. The solids thus retained were washed with dichloromethane (40.0 mL) and the combined organic filtrates concentrated under reduced pressure. The resulting light-brown oil was subjected to flash chromatography (silica gel, 10:0 → 95:5 *v/v* dichloromethane/ammonia-saturated methanol) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.6 in 95:5 *v/v* dichloromethane/ammonia-saturated methanol) afforded compound **3.48** (108 mg, 45%) as a clear, colourless but rather unstable oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.59 (s, 1H), 6.59 (s, 1H), 6.21 (m, 1H), 6.04 (ABq, J = 6.2 Hz, 2H), 5.43 (d, J = 9.9 Hz, 1H), 4.85 (m, 1H), 4.35 (m, 1H), 3.46 (s, 1H), 3.41 (m, 1H), 3.32 (m, 1H), 2.15 (d, J = 15.3 Hz, 1H), 1.84 (d, J = 15.3 Hz, 1H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H) (signal due to N-H group proton not observed);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 163.2, 152.7, 147.7, 136.7, 133.4, 127.2, 117.4, 110.2, 107.3, 102.2, 87.4, 62.8, 61.5, 52.2, 48.3, 28.7, 25.9, 18.1, –4.6, –4.7 (two signals obscured or overlapping);
IR (KBr) ν_{max} 3366, 2928, 1710, 1617, 1481, 1385, 1273, 1056, 1038, 1017, 836, 778 cm^{-1};
MS (ESI, +ve) *m/z* 416 [$(M+H)^+$, 100%];
HRMS (ESI, +ve) $(M+H)^+$, calculated for $C_{22}H_{30}NO_5Si$: 416.1893. Found: 416.1890.

Concentration of the fraction B (R_f = 0.5 in 95:5 *v/v* dichloromethane/ammonium-saturated methanol) afforded a white powder, recrystallization (dichloromethane/hexane) of which gave compound **3.49** (71 mg, 29%) as a white, crystalline solid, m.p. = 191-194 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.43 (s, 1H), 6.83 (s, 1H), 6.15 (ABq, J = 10.4 Hz, 2H), 6.02 (s, 2H), 4.39 (m, 1H), 4.03 (m, 1H), 3.57 (m, 2H), 3.49 (m, 1H), 2.33-1.87 (complex m, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) (signal due to O-H group proton not observed);

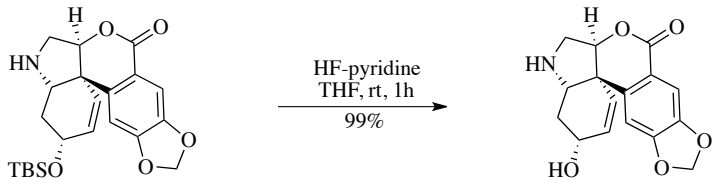
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 181.1, 152.8, 147.0, 146.4, 140.9, 121.9, 121.0, 110.2, 103.2, 102.2, 68.0, 67.7, 58.2, 52.1, 33.2, 26.0, 18.4, –4.4, –4.7 (three signals obscured or overlapping);

IR (KBr) ν_{max} 3467, 2929, 2857, 1683, 1613, 1480, 1264, 1254, 1050, 1029, 803, 772, 728 cm^{-1};

MS (ESI, +ve) *m/z* 416 [$(M+H)^+$, 100];

HRMS (ESI, +ve) $(M+H)^+$, calculated for $C_{22}H_{30}NO_5Si$: 416.1893. Found: 416.1893.

(±)-(3*R*,4a*S*,6a*S*,13b*S*)-3-Hydroxy-4a,5,6,6a-tetrahydro-3*H*-[1,3]dioxolo[4',5':6,7]isochromeno[3,4-*c*]indol-8(4*H*)-one [(±)-3.50]



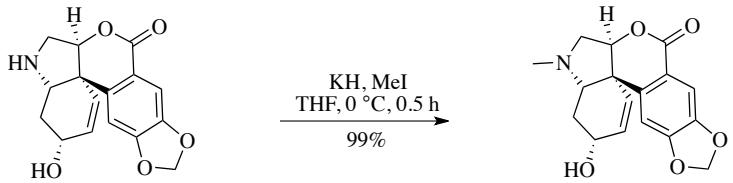
3.48 **3.50**

A magnetically stirred solution of compound **3.48** (20.0 mg, 0.0480 mmol) in tetrahydrofuran (1.00 mL) maintained at 0 °C was treated with HF•pyridine (2.00 µL, 0.0730 mmol,) and the ensuing mixture stirred at this temperature for 0.5 h before being concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 10:0 → 95:5 *v/v* dichloromethane/ammonia-saturated methanol) and concentration of the appropriate fractions (R_f = 0.4 in 95:5 *v/v*

dichloromethane/ammonia-saturated methanol) gave compound **3.50** (14.0 mg, 99%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.55 (s, 1H), 6.64 (s, 1H), 6.49 (m, 1H), 6.04 (m, 2H), 5.46 (d, J = 10.0 Hz, 1H), 4.78 (s, 1H), 4.18 (m, 1H), 3.79 (s, 1H), 3.33 (m, 2H), 2.16 (m, J = 14.8 and 4.1 Hz, 1H), 1.75 (d, J = 14.8 Hz, 1H) (signals due to N-H and O-H group protons not observed);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 163.3, 152.9, 147.9, 136.9, 136.0, 125.5, 116.8, 110.2, 107.6, 102.3, 87.4, 63.2, 60.5, 51.0, 48.2, 29.1;
IR (KBr) ν_{max} 3329, 2919, 1705, 1616, 1480, 1440, 1383, 1272, 1243, 1115, 1057, 1035, 931, 909, 728 cm^{-1};
MS (ESI, +ve) *m/z* 324 (20%), 302 [$(M+H)^+$, 100];
HRMS (ESI, +ve) $(M+H)^+$ calculated for $C_{16}H_{16}NO_5$: 302.1028. Found: 302.1026.

(±)-(3*R*,4a*S*,6a*S*,13b*S*)-3-Hydroxy-5-methyl-4a,5,6,6a-tetrahydro-3*H*-[1,3]dioxolo[4',5':6,7]isochromeno[3,4-*c*]indol-8(4*H*)-one [(±)-3.51]



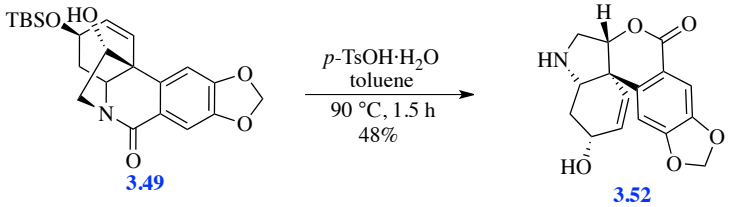
3.50 **3.51**

A magnetically stirred solution of compound **3.50** (10.0 mg, 0.0330 mmol) in tetrahydrofuran (1.00 mL) maintained under a nitrogen atmosphere at 0 °C was treated with potassium hydride (17.6 mg of a 30 wt % dispersion in mineral oil, 0.130 mmol) then methyl iodide (16.5 µL, 0.270 mmol). The ensuing mixture was stirred at 0 °C for 0.5 h then quenched with water (5.00 mL) (CAUTION: POSSIBILITY OF EVOLUTION OF HYDROGEN) before being extracted with ethyl acetate (3 × 10.0 mL). The combined organic phases were washed with brine (1 × 50.0 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 10:0 → 95:5 *v/v* dichloromethane/ammonia-saturated

methanol) and concentration of the appropriate fractions (R_f = 0.5 in 95:5 *v/v* dichloromethane/ammonia-saturated methanol) afforded compound **3.51** (10.0 mg, 99%) as a clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.58 (s, 1H), 6.65 (s, 1H), 6.46 (m, 1H), 6.05 (ABq, J = 4.3 Hz, 2H), 5.45 (d, J = 9.9 Hz, 1H), 4.73 (s, 1H), 4.15 (broad s, 1H), 3.59 (dd, J = 13.0 and 3.2 Hz, 1H), 3.14 (s, 1H), 2.95 (d, J = 13.0 Hz, 1H), 2.58 (s, 3H), 2.20 (broad d, J = 14.9 Hz, 1H), 1.73 (broad d, J = 14.9 Hz, 1H) (signal due to O-H group proton not observed);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 163.1, 152.9, 147.9, 136.6, 135.4, 125.6, 117.1, 110.2, 107.7, 102.4, 86.4, 68.9, 63.3, 59.9, 49.1, 42.7, 26.8;
IR (KBr) ν_{max} 3420, 2919, 1716, 1617, 1482, 1440, 1275, 1247, 1127, 1055, 1036, 932 cm^{-1};
MS (ESI, +ve) *m/z* 338 (69%), 316 [(M+H)$^+$, 100];
HRMS (ESI, +ve) (M+H)$^+$ calculated for $C_{17}H_{18}NO_5$: 316.1185. Found: 316.1183.

(±)-(3*R*,4a*S*,6a*R*,13b*S*)-3-Hydroxy-4a,5,6,6a-tetrahydro-3*H*-[1,3]dioxolo[4',5':6,7]isochromeno[3,4-*c*]indol-8(4*H*)-one [(±)-3.52]

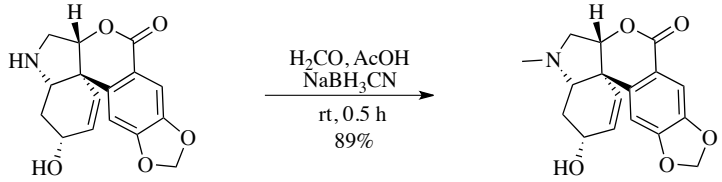


A magnetically stirred solution of compound **3.49** (120 mg, 0.290 mmol) in toluene (5.00 mL) was treated with *p*-toluenesulfonic acid monohydrate (54.9 mg, 0.330 mmol) and the resulting solution stirred at 90 °C for 1.5 h then cooled, quenched with $NaHCO_3$ (10.0 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 × 20.0 mL). The combined organic phases were washed with brine (1 × 100 mL) before being dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue thus obtained was subject to flash column chromatography (silica gel, 10:0 → 95:5 *v/v* dichloromethane/ammonia-saturated methanol) and concentration of the appropriate

fractions (R_f = 0.4 in 95:5 *v/v* dichloromethane/ammonia-saturated methanol) afforded compound **3.52** (42.0 mg, 48%) as a white, crystalline solid, m.p. = 181-184 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.55 (s, 1H), 6.66 (s, 1H), 6.23 (m, 1H), 6.05 (ABq, J = 8.0 Hz, 2H), 5.63 (d, J = 10.2 Hz, 1H), 4.56 (m, 1H), 4.20 (m, 1H), 4.00 (broad s, 1H), 3.28 (m, 1H), 3.08 (t, J = 10.8 Hz, 1H), 2.46 (d, J = 15.1 Hz, 1H), 2.15 (dd, J = 15.1 and 4.8 Hz, 1H) (signals due to O-H and N-H group protons not observed);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 165.1, 152.7, 147.7, 140.9, 132.9, 125.7, 118.4, 111.4, 103.7, 102.4, 82.9, 62.7, 55.6, 44.5, 44.0, 32.8;
IR (KBr) ν_{max} 3335, 2921, 1719, 1615, 1479, 1271, 1246, 1072, 1033, 907, 727 cm^{-1};
MS (ESI, +ve) *m/z* 302 [$(M+H)^+$, 100%];
HRMS (ESI, +ve) $(M+H)^+$ calculated for $C_{16}H_{16}NO_5$: 302.1028. Found: 302.1026.

(±)-(3*R*,4a*S*,6a*R*,13b*S*)-3-Hydroxy-5-methyl-4a,5,6,6a-tetrahydro-3*H*-[1,3]dioxolo[4',5':6,7]isochromeno[3,4-*c*]indol-8(4*H*)-one [(±)-1.68]



3.52 1.68

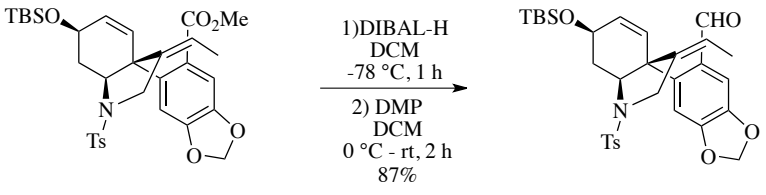
A magnetically stirred solution of compound **3.52** (7.00 mg, 0.0230 mmol) acetonitrile (1.00 mL) maintained at 22 °C was treated, successively, with formalin (17.5 µL of a 37% aqueous solution, 0.210 mmol), acetic acid (5.00 µL, 0.0900 mmol) and $NaBH_3CN$ (5.70 mg, 0.870 mmol). The ensuing mixture was stirred at ambient temperatures for 1 h then quenched with $NaHCO_3$ (5.00 mL of a saturated aqueous solution) before being extracted with ethyl acetate (3 × 15.0 mL). The combined organic phases were washed with brine (1 × 50.0 mL) then dried (Na_2SO_4) and filtered before being concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica gel, 10:0 → 95:5 *v/v* dichloromethane/ammonia-saturated methanol) and concentration of the appropriate fractions (R_f = 0.5 in 95:5 *v/v* dichloromethane/ammonia-saturated

methanol) afforded a powder that was recrystallized (methanol/water) to give compound **1.68** (6.00 mg, 89%) as a white, crystalline solid, m.p. = 199-202 °C.

^{1}H NMR (400 MHz, CD_3OD) δ_H 7.43 (s, 1H), 6.84 (s, 1H), 6.14 (dd, J = 10.1 and 5.2 Hz, 1H), 6.08 (ABq, J = 1.0 Hz, 2H), 5.57 (dd, J = 10.2 and 1.4 Hz, 1H), 4.71 (m, 1H), 4.30 (s, 1H), 4.12 (m, 1H), 3.37 (m, 1H), 3.25 (m, 1H), 2.90 (m, 1H), 2.58 (s, 3H), 2.44 (m, 1H), 2.23 (m, 1H);
^{13}C NMR (100 MHz, CD_3OD) δ_C 167.2, 154.3, 148.9, 143.1, 133.1, 127.2, 119.4, 111.3, 104.9, 103.9, 82.0, 65.6, 64.4, 53.7, 47.5, 42.9, 31.1;
IR (KBr) ν_{max} 3267, 2920, 2877, 2852, 1723, 1615, 1480, 1276, 1247, 1026 cm^{-1};
MS (ESI, +ve) *m/z* 316 [$(M+H)^+$, 100%], 298 (80);
HRMS (ESI, +ve) $(M+H)^+$ calculated for $C_{17}H_{18}NO_5$: 316.1185. Found: 316.1182.

5.4 Experimental Procedures Related to Work Described in Chapter Four

(±)-6-((3a*R*,6*R*,7a*S*,*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-3-ethylidene-1-tosyl-2,3,3a,6,7,7a-hexahydro-1*H*-indol-3a-yl)benzo[*d*][1,3]dioxole-5-carbaldehyde [(±)-4.1]



3.16 **4.1**

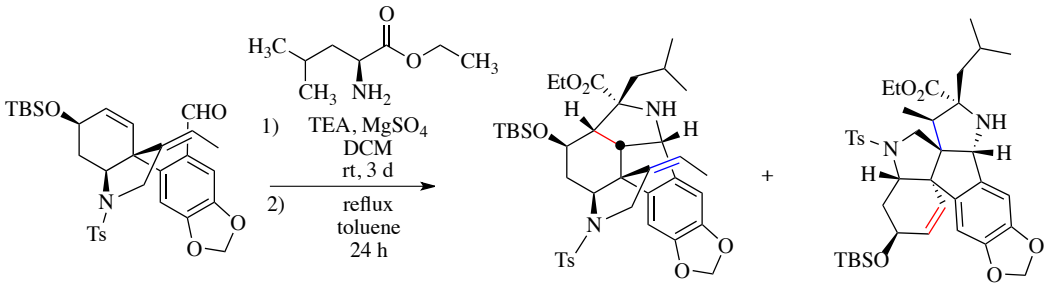
Step i: A magnetically stirred solution of compound **3.16** (500 mg, 0.820 mmol) in dichloromethane (35.0 mL) maintained under nitrogen was cooled to −78 °C then treated, dropwise, with DIBAl-H (2.05 mL of a solution 1 M in tetrahydrofuran, 2.05 mmol). The resulting mixture was stirred at −78 °C for 1 h then quenched with tartaric acid (20.0 mL of a 1 M aqueous solution) and the ensuing mixture stirred for 0.5 h while being allowed to warm to 22 °C. The separated aqueous phase was extracted with dichloromethane (2 × 30.0

mL) and the combined organic phases then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting clear, colourless oil was subjected to flash chromatography (silica gel, 4:1 *v/v* hexane/ethyl acetate) to give, after concentration of the relevant fractions (R_f = 0.5 in 7:3 *v/v* hexane/ethyl acetate), a white solid. This material, assumed to be the anticipated benzyl alcohol, was subjected, without purification, to *step ii* of the reaction sequence as detailed immediately below.

Step ii: The solid obtained from *step i* was dissolved in dry dichloromethane (20.0 mL) and the resulting solution cooled to 0 °C then treated with the Dess-Martin periodinane (345 mg, 0.820 mmol). The ensuing mixture was stirred at 0 °C for 0.5 h then quenched with brine (10.0 mL). The separated aqueous phase was extracted with dichloromethane (2 × 20.0 mL) and the organic phases then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash chromatography (silica gel, 4:1 *v/v* hexane/ethyl acetate) to afford, after concentration of the appropriate fractions (R_f = 0.6 in 7:3 *v/v* hexane/ethyl acetate), compound **4.1** (415 mg, 87%) as a white, crystalline solid, m.p. = 188-190 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.21 (s, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.22 (s, 1H), 6.99 (d, J = 8.2 Hz, 2H), 6.41 (s, 1H), 5.99 (s, 1H), 5.91 (s, 1H), 5.72 (m, 2H), 5.50 (m, 1H), 4.54 (m, 1H), 4.35 (m, 2H), 3.87 (dd, J = 14.2 and 1.2 Hz, 1H), 2.39 (m, 1H), 2.35 (s, 3H), 1.80 (m, 4H), 0.91 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 188.6, 151.5, 147.2, 143.5, 142.8, 141.2, 135.5, 131.3, 130.9, 129.4, 129.1, 126.6, 124.7, 109.6, 109.0, 102.1, 67.6, 67.4, 54.2, 48.1, 39.6, 26.0, 21.5, 18.3, 14.9, –4.3, –4.5 (four signals obscured or overlapping);
IR (KBr) ν_{max} 2954, 2928, 2856, 1673, 1612, 1505, 1482, 1342, 1253, 1158, 1093, 1065, 1038, 932, 872, 835, 664 cm^{-1};
MS (ESI, +ve) *m/z* 604 [$(M+Na)^+$, 100%];
HRMS (ESI, +ve) $(M + Na)^+$, calculated for $C_{31}H_{39}NNaO_6SSi$: 604.2165. Found: 604.2169.

(±)-(3a*S*,5*R*,5a*S*,6*R*,7a*S*,12b*R*,*Z*)-Ethyl 5-((*tert*-Butyldimethylsilyl)oxy)-1-ethylidene-6-isobutyl-3-tosyl-2,3,3a,4,5,5a,5a^{1},6,7,7a-decahydro-1*H*-[1,3]dioxolo[4',5':5,6]indeno[1,2,3-*cd*]pyrrolo[3,2-*e*]isoindole-6-carboxylate [(±)-4.3] and (±)-(3*S*,4a*S*,6a*S*,7*R*,8*R*,9a*R*,14b*R*)-Ethyl 3-((*tert*-Butyldimethylsilyl)oxy)-8-isobutyl-7-methyl-5-tosyl-4,4a,5,6,7,8,9,9a-octahydro-3*H*-[1,3]dioxolo[4',5':5,6]pyrrolo[3',2':2,3]indeno[2,1-*c*]indole-8-carboxylate [(±)-4.4]



4.1 **4.3** 38% **4.4** 36%

A magnetically stirred solution of compound **4.1** (300 mg, 0.520 mmol, 1.0 equiv.) in dichloromethane (20.0 mL) maintained under a nitrogen atmosphere at 22 °C was treated with *L*-Leu-OEt•HCl (305 mg, 1.56 mmol), triethylamine (125 μL, 0.870 mmol) and anhydrous $MgSO_4$ (300 mg, 7.82 mmol). The ensuing mixture was stirred at 22 °C for 18 h then concentrated under reduced pressure. The residue thus obtained was treated with toluene (20.0 mL) and the resulting suspension heated under reflux for 24 h before being cooled then concentrated under reduced pressure. The residue was subjected to flash chromatography (silica gel, 9:1 → 4:1 *v/v* hexane/ethyl acetate) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.6 in 7:3 *v/v* hexane/ethyl acetate) afforded compound **4.3** (134 mg, 36%) as white, crystalline solid, m.p. = 210-212 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.79 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 6.63 (s, 1H), 5.83 (m, 2H), 5.29 (s, 1H), 5.05 (m, 1H), 4.70 (d, J = 7.9 Hz, 1H), 4.49 (m, 1H), 4.10 (m, 2H), 3.86 (m, 1H), 3.74 (m, 1H), 3.67 (m, 1H), 3.24 (dd, J = 11.0 and 7.9 Hz, 1H), 2.45

(s, 3H), 2.35-2.33 (complex m, 1H), 2.11 (m, 1H), 1.97 (dd, J = 14.1 and 5.5 Hz, 1H), 1.62 (m, 1H), 1.51 (d, J = 6.9 Hz, 3H), 1.49-1.40 (complex m, 2H), 1.14 (t, J = 7.2 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 0.87 (s, 9H), 0.82 (d, J = 6.6 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H) (signal due to N-H group proton not observed);

^{13}C NMR (400 MHz, $CDCl_3$) δ_C 174.3, 148.5, 147.5, 146.3, 144.0, 143.1, 136.3, 134.4, 130.0, 127.4, 117.7, 104.7, 102.3, 101.3, 71.1, 66.4, 66.1, 64.6, 60.9, 58.4, 57.8, 51.5, 48.7, 48.5, 37.8, 26.1, 25.4, 24.1(4), 24.0(7), 21.7, 18.2, 14.9, 14.0, –3.6, –4.2 (four signals obscured or overlapping);

IR (KBr) ν_{max} 2955, 2929, 2858, 1721, 1598, 1474, 1345, 1258, 1218, 1160, 1065, 1040, 941, 834, 662 cm^{-1};

MS (ESI, +ve) *m/z* 723 [(M+H)+, 100%];

HRMS (ESI, +ve) $(M + H)^+$, calculated for $C_{39}H_{55}N_2O_7SSi$: 723.3499. Found: 723.3494.

Concentration of fraction B (R_f = 0.5 in 7:3 *v/v* hexane/ethyl acetate) afforded compound **4.4** (142 mg, 38%) as clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H), 6.46 (s, 1H), 6.21 (s, 1H), 5.97 (d, J = 1.3 Hz, 1H), 5.89 (d, J = 1.3 Hz, 1H), 5.77 (d, J = 10.2 Hz, 1H), 5.20 (d, J = 10.2 Hz, 1H), 4.39 (m, 1H), 4.14 (ABq, J = 7.1 Hz, 2H), 3.99 (dd, J = 12.8 and 4.6 Hz, 1H), 3.83 (s, 1H), 3.79 (d, J = 11.6 Hz, 1H), 3.41 (d, J = 11.6 Hz, 1H), 2.36 (s, 3H), 2.26 (m, 1H), 2.17 (m, 1H), 1.74 (m, 3H), 1.45 (m, 1H), 1.25 (t, J = 7.4 Hz, 3H), 1.20 (m, 1H), 1.04 (d, J = 7.4 Hz, 3H), 1.00 (d, J = 6.4 Hz, 3H), 0.90 (s, 9H), 0.81 (d, J = 6.4 Hz, 3H), 0.11 (s, 3H), 0.09 (s, 3H);

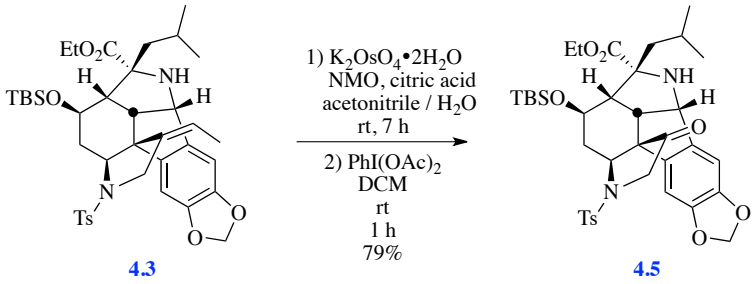
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.9, 148.9, 148.1, 143.1, 140.7, 136.7, 134.7, 134.3, 129.3, 129.2, 126.8, 104.8, 104.4, 101.5, 76.6, 73.5, 67.8, 66.6, 64.0, 62.5, 61.3, 53.9, 48.9, 38.2, 37.3, 26.0, 24.9, 24.7, 22.6, 21.5, 18.3, 14.2, 11.4, –4.4, –4.5 (four signals obscured or overlapping);

IR (KBr) ν_{max} 2953, 2927, 2865, 1727, 1475, 1331, 1246, 1162, 1090, 1041, 937, 878, 835, 777, 664 cm^{-1};

MS (ESI, +ve) *m/z* 745 (55%), 723 $[(M+H)^+$, 100];

HRMS (ESI, +ve) $(M + H)^+$, Calculated for $C_{39}H_{55}N_2O_7SSi$: 723.3499. Found: 723.3485.

(±)-(3a*S*,5*R*,5a*S*,6*R*,7a*S*,12b*S*)-Ethyl 5-((*tert*-Butyldimethylsilyl)oxy)-6-isobutyl-1-oxo-3-tosyl-2,3,3a,4,5,5a,5a[1],6,7,7a-decahydro-1*H*-[1,3]dioxolo[4',5':5,6]indeno[1,2,3-*cd*]pyrrolo[3,2-*e*]isoindole-6-carboxylate [(±)-4.5]



4.3 4.5

Step i: A magnetically stirred solution of compound **4.3** (150 mg, 0.210 mmol) in acetonitrile/water (15.0 mL of a 4:1 *v/v* mixture) maintained at 22 °C was treated with citric acid (99.0 mg, 0.510 mmol), *N*-methylmorpholine *N*-oxide (72.0 mg, 0.420 mmol) and potassium osmate dihydrate (8.00 mg, 0.0200 mmol). The ensuing mixture was stirred vigorously at 22 °C for 7 h then diluted with ethyl acetate (10.0 mL) and water (10.0 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 10.0 mL) and the combined organic phases then washed with brine (1 × 20.0 mL) before being dried (MgSO4), filtered and concentrated under reduced pressure. The resulting light-brown oil was subject to flash chromatography (silica gel, 2% ammonia saturated methanol in dichloromethane) to afford, after concentration of the relevant fractions (R_f = 0.5 in 19:1 *v/v* dichloromethane/ammonia-saturated methanol), a clear, colourless oil. This material was subjected to step ii of the reaction sequence as detailed immediately below.

Step ii: A solution of the oil obtained as described above in *step i* was dissolved in dichloromethane (1.50 mL) and the solution thus formed treated with iodobenzene diacetate (81.0 mg, 0.250 mmol). The ensuing mixture was stirred vigorously at 22 °C for 2 h before being treated with TLC-grade silica gel (100 mg) then concentrated under reduced pressure. The resulting free-flowing solid was subjected to flash chromatography (silica gel, 4:1 *v/v* hexane/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.6 in

7:3 *v/v* hexane/ethyl acetate) afforded the title compound **4.5** (119 mg, 79%) as white, crystalline solid, m.p. = 215-216 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 6.69 (s, 1H), 5.84 (m, 2H), 4.88 (s, 1H), 4.45 (d, J = 6.6 Hz, 1H), 4.32 (broadened s, 1H), 4.25-4.10 (complex m, 1H), 4.11-3.97 (complex m, 2H), 3.93 (d, J = 1.7 Hz, 2H), 3.49 (m, 1H), 2.45 (s, 3H), 2.32 (dd, J = 10.1 and 3.4 Hz, 1H), 2.05 (m, 1H), 1.91 (m, 1H), 1.87-1.72 (complex m, 3H), 1.67 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H), 0.88 (s, 9H), 0.82 (d, J = 6.6 Hz, 3H), 0.99 (s, 3H), 0.97 (s, 3H);

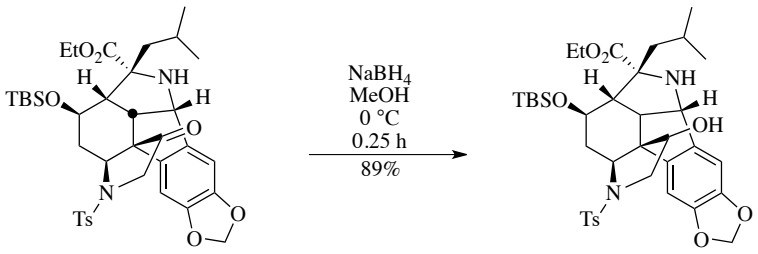
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 210.8, 174.2, 148.7, 147.7, 144.7, 140.0, 135.1, 134.7, 130.3, 127.5, 105.6, 102.3, 101.5, 73.3, 65.6, 65.0, 63.0, 61.2, 60.2, 53.9, 52.9, 48.1, 47.7, 34.4, 26.0, 24.8, 24.6, 23.1, 21.8, 18.6, 14.2, –4.6, –4.7 (four signals obscured or overlapping);

IR (KBr) ν_{max} 2941, 2929, 2861, 1760, 1726, 1477, 1351, 1254, 1159, 1066, 1039, 941, 834, 663, 586 cm^{-1};

MS (ESI, +ve) *m/z* 733 (65%), 711 [$(M+H)^+$, 100%];

HRMS (ESI, +ve) $(M + H)^+$, Calculated for $C_{37}H_{51}N_2O_8SSi$: 711.3135. Found: 711.3127.

(±)-(1*S*,3a*S*,5*R*,5a*S*,6*R*,7a*S*,12b*S*)-Ethyl 5-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-6-isobutyl-3-tosyl-2,3,3a,4,5,5a,5a^1,6,7,7a-decahydro-1*H*-[1,3]dioxolo[4',5':5,6]indeno[1,2,3-*cd*]pyrrolo[3,2-*e*]isoindole-6-carboxylate [(±)-4.6]



4.5 **4.6**

A magnetically stirred solution of compound **4.5** (150 mg, 0.211 mmol) in methanol (10.0 mL) maintained at 22 °C was treated with sodium borohydride (8.50 mg, 0.230 mmol) and the ensuing mixture stirred for 0.5 h then diluted with ethyl acetate (10.0 mL) and water (5.00 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 10.0 mL) and

the combined organic phases were washed with brine (1 × 20.0 mL) before being dried (MgSO4), filtered and concentrated under reduced pressure. The resulting clear, colourless oil was subjected to flash chromatography (silica gel, 4:1 *v/v* hexane/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.3 in 7:3 *v/v* hexane/ethyl acetate) afforded the title compound **4.6** (134 mg, 89%) as white, crystalline solid, m.p. = 218-219 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.77 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 6.68 (s, 1H), 5.85 (m, 2H), 4.93 (s, 1H), 4.60 (d, *J* = 7.7 Hz, 1H), 4.39 (m, 1H), 4.20 (m, 1H), 3.85-3.78 (complex m, 1H), 3.78-3.70 (complex m, 1H), 3.70-3.61 (complex m, 1H), 3.54 (m, 1H), 3.11 (dd, *J* = 10.8 and 7.8 Hz, 1H), 2.97 (t, *J* = 9.2 Hz, 1H), 2.46 (s, 3H), 2.38-2.32 (complex m, 2H), 1.98 (dd, *J* = 14.1 and 5.4 Hz, 1H), 1.69 (m, 1H), 1.60 (m, 1H), 1.43 (m, 1H), 1.13 (t, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.12 (s, 3H), 0.09 (s, 3H) (signal due to N-H and O-H protons not observed);

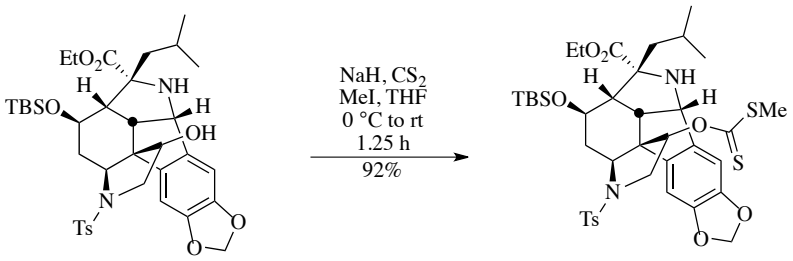
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.2, 148.4, 148.3, 144.5, 138.9, 134.7, 133.9, 130.1, 127.8, 105.5, 103.3, 101.5, 78.6, 71.0, 66.5, 65.7, 62.9, 60.8, 58.3, 57.8, 51.9, 50.7, 48.3, 39.3, 26.2, 25.4, 24.2, 24.1, 21.8, 18.3, 14.0, –3.5, –3.9 (four signals obscured or overlapping);

IR (KBr) ν_{max} 3499, 2953, 2929, 2858, 1720, 1598, 1474, 1347, 1256, 1159, 1067, 1039, 940, 833, 665 cm^{-1};

MS (ESI, +ve) *m/z* 735 (51%), 713 [$(M+H)^+$, 100];

HRMS (ESI, +ve) $(M + H)^+$, Calculated for $C_{37}H_{53}N_2O_8SSi$: 713.3292. Found: 713.3291.

(±)-(1*S*,3a*S*,5*R*,5a*S*,6*R*,7a*S*,12b*S*)-Ethyl 5-((*tert*-Butyldimethylsilyl)oxy)-6-isobutyl-1-(((methylthio)carbonothioyl)oxy)-3-tosyl-2,3,3a,4,5,5a,5a^{1},6,7,7a-decahydro-1*H*-[1,3]dioxolo[4',5':5,6]indeno[1,2,3-*cd*]pyrrolo[3,2-*e*]isoindole-6-carboxylate [(±)-4.7]



4.6 4.7

A magnetically stirred solution of alcohol **4.6** (50.0 mg, 0.0700 mmol) in dry tetrahydrofuran (10.0 mL) maintained at 0 °C under a nitrogen atmosphere was treated with sodium hydride (2.00 mg of a 60% dispersion in mineral oil, 0.0830 mmol). After 0.25 h carbon disulfide (100 μL, 1.70 mmol) then methyl iodide (110 μL, 1.70 mmol) were added to the reaction mixture. The ensuing mixture was allowed to warm to 22 °C and stirred for 1 h at this temperature before being treated with water (10.0 mL) then extracted with ethyl acetate (3 × 10.0 mL). The combined organic phases were washed with brine (1 × 20.0 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica gel, 4:1 *v/v* hexane/ethyl acetate) and concentration of the appropriate fractions (R_f = 0.7 in 7:3 *v/v* hexane/ethyl acetate) afforded the title compound **4.7** (52.0 mg, 92%) as colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 6.65 (s, 1H), 5.85 (dd, *J* = 9.4, 1.4 Hz, 2H), 5.76 (t, *J* = 5.9 Hz, 1H), 5.38 (s, 1H), 4.59 (d, *J* = 7.5 Hz, 1H), 4.36 (dt, *J* = 8.3, 4.2 Hz, 1H), 4.08 (dd, *J* = 11.1, 6.0 Hz, 1H), 3.93-3.84 (complex m, 1H), 3.76-3.66 (complex m, 2H), 3.36 (dd, *J* = 11.1, 5.9 Hz, 1H), 3.07 (dd, *J* = 10.9, 7.5 Hz, 1H), 2.45 (s, 3H), 2.39 (dd, *J* = 10.9, 4.8 Hz, 1H), 2.13 (s, 3H), 2.08-1.92 (complex m, 3H), 1.60 (dt, *J* = 12.8, 6.5 Hz, 1H), 1.52-1.41 (complex m, 1H), 1.14 (t, *J* = 7.2 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.91 (s, 9H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.14 (s, 3H), 0.11 (s, 3H) (signal due to N-H group proton not observed);

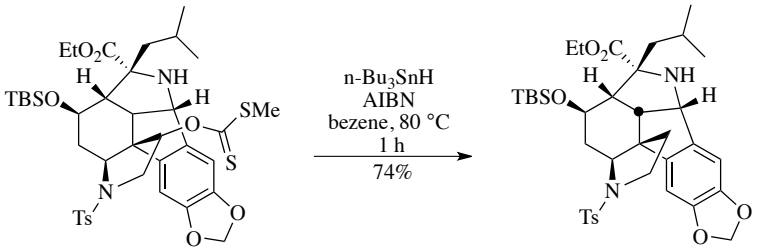
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 214.62, 174.06, 147.87, 147.83, 144.15, 137.46, 135.71, 134.04, 129.98, 127.60, 104.94, 103.87, 101.21, 86.86, 71.22, 65.68, 65.64, 61.64, 60.65, 57.04, 56.23, 49.96, 49.41, 48.84, 36.11, 26.07, 25.16, 24.08, 23.82, 21.63, 18.44, 18.23, 13.86, –3.99, –4.39 (four signals obscured or overlapping);

IR (KBr) ν_{max} 3499, 2953, 2929, 2858, 1720, 1598, 1474, 1347, 1256, 1159, 1067, 1039, 940, 833, 665 cm^{-1};

MS (ESI, +ve) *m/z* 735 (51%), 713 [$(M+H)^+$, 100];

HRMS (ESI, +ve) $(M + H)^+$, Calculated for $C_{37}H_{53}N_2O_8SSi$: 713.3292. Found: 713.3291.

(±)-(3a*S*,5*R*,5a*S*,6*R*,7a*S*,12b*R*)-Ethyl 5-((*tert*-Butyldimethylsilyl)oxy)-6-isobutyl-3-tosyl-2,3,3a,4,5,5a,5a^1,6,7,7a-decahydro-1*H*-[1,3]dioxolo[4',5':5,6]indeno[1,2,3-*cd*]pyrrolo[3,2-*e*]isoindole-6-carboxylate [(±)-4.8]



4.7 4.8

A magnetically stirred solution of xanthate **4.7** (52.0 mg, 0.0650 mmol) in benzene (5.00 mL) and the resulting solution deoxygenated using nitrogen then treated with 2,2'-azobis(*iso*-butyronitrile) (3.50 mg, 0.0200 mmol), tri-*n*-butyltin hydride (37.0 μL, 0.140 mmol) before being heated under reflux for 1 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 4:1 *v/v* hexane/ethyl acetate). Concentration of the appropriate fractions (R_f = 0.4 in 7:3 *v/v* hexane/ethyl acetate) gave compound **4.8** (33.0 mg, 73%) as clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.79 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 6.64 (s, 1H), 5.82 (m, 2H), 4.88 (s, 1H), 4.61 (d, J = 7.5 Hz, 1H), 4.40 (m, 1H), 3.90-3.79 (complex

m, 1H), 3.67 (m, 1H), 3.58 (m, 1H), 3.42 (dd, *J* = 10.4 and 4.6 Hz, 1H), 3.23 (m, 1H), 3.00 (dd, *J* = 10.8 and 7.9 Hz, 1H), 2.47 (s, 3H), 2.35 (m, 2H), 2.14 (m, 1H), 1.99 (dd, *J* = 14.1 and 5.4 Hz, 1H), 1.72-1.56 (complex m, 3H), 1.44 (m, 1H), 1.13 (t, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.13 (s, 3H), 0.11 (s, 3H) (signal due to N-H group proton not observed);

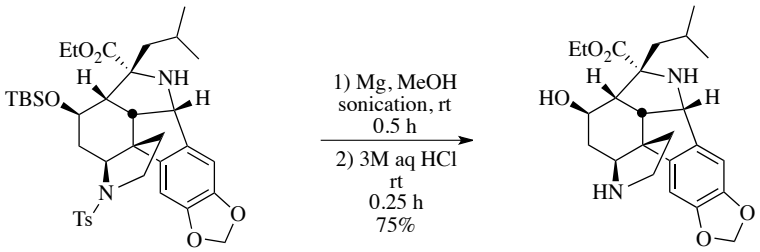
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 174.1, 148.1, 147.3, 144.1, 142.0, 135.2, 134.3, 129.9, 127.5, 104.9, 102.0, 101.1, 70.9, 66.5, 65.7, 63.5, 60.6, 58.0, 54.5, 51.9, 48.2, 46.7, 41.9, 39.3, 26.0, 25.3, 24.0(4), 23.9(9), 21.6, 18.2, 13.8, –3.6, –4.1 (four signals obscured or overlapping);

IR (KBr) ν_{max} 2951, 2928, 2860, 1721, 1474, 1347, 1258, 1162, 1040, 862, 836, 665 cm^{-1};

MS (ESI, +ve) *m/z* 697 [$(M+H)^+$, 72%,], 245 (100);

HRMS (ESI, +ve) $(M + H)^+$, Calculated for $C_{37}H_{53}N_2O_7SSi$: 697.3343. Found: 697.3345.

(±)-(3a*S*,5*R*,5a*S*,6*R*,7a*S*,12b*R*)-Ethyl 5-Hydroxy-6-isobutyl-2,3,3a,4,5,5a,5a^1,6,7,7a-decahydro-1*H*-[1,3]dioxolo[4',5':5,6]indeno[1,2,3-*cd*]pyrrolo[3,2-*e*]isoindole-6-carboxylate [(±)-4.9]



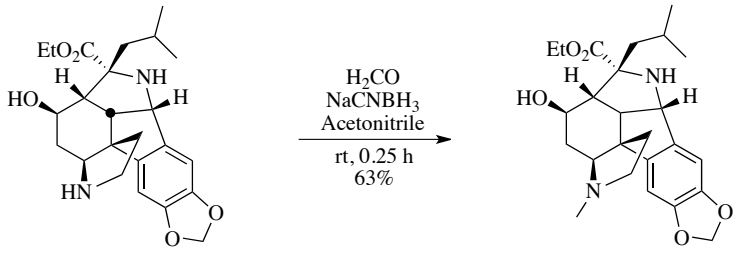
4.8 **4.9**

A solution of compound **4.8** (50.0 mg, 0.0700 mmol) in methanol (10.0 mL) maintained at 22 °C under a nitrogen atmosphere was treated with magnesium metal (20.0 mg, 0.820 mmol). The ensuing mixture was subject to sonication for 0.5 h in an ultrasonic cleaning bath operating at 50 kHz bath then quenched with hydrochloric acid (5.00 mL of a 3 M aqueous solution) before being stirred magnetically for 0.25 h then partitioned between water (10.0 mL) and ethyl acetate (10.0 mL). The separated aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic phases were washed with brine (1

× 10.0 mL) then dried (MgSO4), filtered and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 19:1 *v/v* dichloromethane/ammonia-saturated methanol) and concentration of the appropriate fractions (R_f = 0.2 in 9:1 *v/v* dichloromethane/ammonia-saturated methanol) afforded the title compound **4.9** (23.0 mg, 75%) as clear, colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.78 (s, 1H), 6.52 (s, 1H), 5.93 (m, 2H), 4.76 (d, J = 7.8 Hz, 1H), 3.95-3.80 (complex m, 3H), 3.57 (t, J = 4.6 Hz, 1H), 3.17-3.06 (complex m, 2H), 3.01 (dd, J = 10.9 and 7.8 Hz, 1H), 2.52 (dd, J = 11.0 and 4.0 Hz, 1H), 2.04 (dd, J = 13.8 and 5.8 Hz, 1H), 1.94 (t, J = 7.0 Hz, 2H), 1.82 (m, 1H), 1.68-1.51 (complex m, 3H), 1.16 (t, J = 7.2 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 0.87 (m, 1H), 0.83 (d, J = 6.4 Hz, 3H) (signals due to O-H and N-H group protons not observed);
^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.0, 148.4, 147.5, 141.4, 136.4, 105.4, 102.3, 101.3, 72.8, 67.0, 66.4, 61.5, 60.9, 57.2, 52.9, 50.2, 49.7, 46.1, 44.5, 31.6, 25.4, 24.3, 23.7, 14.0;
IR (KBr) ν_{max} 3319, 2943, 2862, 1719, 1476, 1368, 1319, 1252, 1229, 1147, 1039, 939, 862, 731 cm^{-1};
MS (ESI, +ve) *m/z* 429 [$(M+H)^+$, 100%];
HRMS (ESI, +ve) $(M + H)^+$, Calculated for $C_{24}H_{33}N_2O_5$: 429.2389. Found: 429.2389.

(±)-Gracilamine [(±)-1.1]



4.9 (±)-**1.1**

A magnetically stirred solution of compound **4.9** (23.0 mg, 0.0540 mmol) in acetonitrile (10.0 mL) was treated with formaldehyde (4.50 µL of a 35% w/w aqueous solution, 0.0500 mmol) and sodium cyanoborohydride (3.30 mg, 0.0500 mmol). The resulting mixture was

stirred at room temperature for 0.25 h then quenched with $NaHCO_3$ (10.0 mL of a saturated aqueous solution). The separated aqueous phase was extracted with ethyl acetate (3 × 20.0 mL) and the combined organic phases were washed with brine (1 × 20.0 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting brown oil was subjected to flash chromatography (silica gel, 98:2 *v/v* dichloromethane/ammonia-saturated methanol) and concentration of the appropriate fractions (R_f = 0.7 in 9:1 *v/v* dichloromethane/ammonia-saturated methanol) afforded compound (±)-**1.1** (15.1 mg, 63%) as a colourless, crystalline solid, m.p. = 212-213 °C (lit.[22] m.p. = 188-191 °C).

^{1}H NMR (700 MHz, CD_3OD) δ_H 6.85 (s, 1H), 6.67 (s, 1H), 5.93 (m, 2H), 4.65 (d, *J* = 8.0 Hz, 1H), 4.00-3.95 (complex m, 2H), 3.41 (m, 1H), 3.15 (dd, *J* = 9.9 and 8.0 Hz, 1H), 3.11 (m, 1H), 2.81 (broadened s, 1H), 2.56 (m, 1H), 2.48 (s, 3H), 2.27 (dd, *J* = 9.9 and 8.8 Hz, 1H), 2.03 (m, 1H), 1.96 (m, 2H), 1.84 (m, 1H), 1.73 (m, 1H), 1.65 (dd, *J* = 14.1 and 5.4 Hz, 1H), 1.54 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H) (signals due to hydroxyl and amine group protons not observed);

^{13}C NMR (175 MHz, CD_3OD) δ_C 175.8, 150.1, 149.1, 144.4, 136.4, 105.8, 103.7, 102.7, 74.2, 71.3, 67.7, 66.5, 62.1, 58.8, 56.6, 55.6, 54.7, 47.7, 45.3, 40.8, 35.5, 26.3, 24.9, 23.6, 14.1;

IR (KBr) ν_{max} 3331, 2947, 2865, 2784, 1721, 1501, 1476, 1368, 1232, 1145, 1038, 940, 861 cm^{-1};

MS (ESI, +ve) *m/z* 465 (15%), 443 [$(M+H)^+$, 100];

HRMS (ESI, +ve) $(M + H)^+$, calculated for $C_{25}H_{35}N_2O_5$: 443.2546. Found: 443.2547.

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